1st ALPINE WINTER CONFERENCE ON MEDICINAL AND SYNTHETIC CHEMISTRY

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BOOK OF ABSTRACTS

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SPEAKERS & ORAL COMMUNICATIONS

Biographies and Abstracts

Erick M. CARREIRA

ETH Zürich, Switzerland

Prof. Erick M. Carreira obtained a B.S. degree in 1984 from the University of Illinois at Urbana-Champaign under the supervision of Scott E. Denmark and a Ph.D. degree in 1990 from Harvard University under the supervision of David A. Evans. After carrying out postdoctoral work with Peter Dervan at the California Institute of Technology through late 1992, he joined the faculty at the same institution as an assistant professor of chemistry and subsequently was promoted to the rank of associate professor in the Spring of 1996, and full professor in Spring 1997. Since September 1998, he has been professor of chemistry at the ETH Zürich in the Institute of Organic Chemistry. In 2011, he became associated with the Competence Center for Systems Physiology and Metabolic Diseases at ETH-Zürich.

He is the recipient of numerous awards. Professor Carreira's interests encompass several facets of chemical synthesis: natural products synthesis, chemistry as well as biology, catalysis, medicinal chemistry, and synthetic methods.

RECENT DEVELOPMENTS IN STRATEGIES AND TACTICS TOWARDS THE SYNTHESIS OF COMPLEX SECONDARY METABOLITES AS ENABLING TOOLS FOR THE STUDY OF BIOLOGY AND MEDICINE

Erick Carreira

ETH Zürich, Vladimir Prelog Weg 3 HCI H335 Zurich 8093 Switzerland

The talk will include discussion and analysis of recent natural product targets that have been synthesized. The methods involve novel, unexpected reactivity and unusual building blocks that are fully integrated to lead to efficient routes. Studies of natural products present in humans highlight new opportunities for the study of human biology and the discovery of new therapies.

Varinder K. AGGARWAL

University of Bristol, United Kingdom

Varinder K. Aggarwal studied chemistry at Cambridge University and received his Ph.D. in 1986 under the guidance of Dr. Stuart Warren. After postdoctoral studies (1986-1988) under Prof. Gilbert Stork, Columbia University, he returned to the UK as a Lecturer at Bath University. In 1991 he moved to Sheffield University, where he was promoted to Professor in in 1997. In 2000 he moved to Bristol University where he holds the Chair in Synthetic Chemistry.

He was elected Fellow of the Royal Society in 2012.

ASSEMBLY LINE SYNTHESIS

Varinder Aggarwal

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Nature has evolved highly sophisticated machinery for organic synthesis, many of which resemble molecular assembly-line processes. So far chemists have been able to apply this type of approach in the synthesis of peptides and oligonucleotides but in these reactions, simple amide (C–N) or phosphate (P–O) bonds are created. It is much more difficult to make C–C bonds but this is central to the discipline of organic synthesis. Here we describe the application of iterative homologation of boronic esters using chiral lithiated benzoate esters and chloromethyllithium to the highly efficient syntheses of several natural products. I will also show how the methodology can be used to determine the structure of natural products which have been incorrectly assigned.

Secondary and tertiary boronic esters are versatile intermediates and can be transformed into alcohols, alkenes, and amines. I will show how this can be expanded to include new coupling reactions with a broad range of aromatics, and also new reactions that convert the boronic ester moiety into a host of other functional groups with full stereocontrol.[5]

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Thorsten BACH

Technical University of Munich, Germany

Thorsten Bach obtained his education at the University of Heidelberg and at the University of Southern California (USC). He received his Ph.D. in 1991 from the University of Marburg with M. T. Reetz and did post-doctoral work with D. A. Evans at Harvard University. He completed his Habilitation at the University of Münster in 1996, moved to the University of Marburg as an associate professor in 1997 and was appointed to the Chair of Organic Chemistry I at the Technische Universität München (TUM) in 2000.

He is an elected member of the German Academy of Sciences (Leopoldina) and of the Bavarian Academy of Sciences.

PHOTOCHEMICAL REACTIONS EN ROUTE TO STRUCTURALLY COMPLEX MOLECULE

Thorsten Bach

Department Chemie and Catalysis Research Center (CRC), Technische Universität München, D-85747 Garching, Germany

Photochemical reactions provide ready access to structurally unique compounds that are often relevant to the synthesis of natural products.[1] In recent years, the aspect of enantioselectivity has received increasing attention from the photochemical community and notable progress has been made.[2] Our group has been active in the field for some time with a particular focus on [2+2] photocycloaddition chemistry.[3] The presentation will cover our work and will provide the latest results of our research efforts.

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Paolo MELCHIORRE

Institute of Chemical Research of Catalonia, Spain

Paolo Melchiorre studied Chemistry at the University of Bologna – Alma Mater Studiorum (Italy), where he graduated in 1999. He received his PhD in Chemistry in 2003 at Bologna University working in the area of asymmetric catalysis, under the direction of Professor Achille Umani-Ronchi and the supervision of Professor Pier Giorgio Cozzi.In 2002, he spent a period in Denmark working with Professor Karl Anker Jørgensen at the "Center for Catalysis", Århus University, where his studies centered on asymmetric organocatalysis. From 2003, Paolo worked as a postdoctoral associate with Professor Giuseppe Bartoli, at the Industrial Chemistry Faculty of the Bologna University. In October 2007 he took a permanent position as an Assistant Professor at Bologna University. In September 2009 Paolo joined the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona as an ICREA (Catalan Institution of Research and Advanced Studies) Professor and ICIQ Group Leader.

His current scientific interests lie on the discovery and mechanistic elucidation of new asymmetric organocatalytic and photochemical processes that address unsolved problems in synthetic methodology. The final aim is to develop environmentally friendly and innovative catalytic methods that will find widespread use in organic synthesis.

EXPANDING THE POTENTIAL OF ORGANOCATALYSIS WITH LIGHT

Paolo Melchiorre (1,2)

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Light-driven processes considerably enrich the modern synthetic repertoire, offering a potent way to build complex organic frameworks (1). In contrast, it is difficult to develop enantioselective catalytic photoreactions that can create chiral molecules with a well-defined three-dimensional arrangement (2). Recently, our research laboratories (3) has started a program aimed at translating the effective tools governing the success of ground state asymmetric organocatalysis into the realm of photochemical reactivity, exploiting the potential of key organocatalytic intermediates to directly participate in the photoexcitation of substrates. At the same time, the chiral organocatalyst can ensure effective stereochemical control. This single catalyst system, where stereoinduction and photoactivation merge in a sole organocatalyst, can serve for developing novel enantioselective photoreactions. The new synthetic possibilities, opened up by the application of organocatalysis within photochemical and radical patterns, will be discussed (4).

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Peter O'BRIEN

University of York, United Kingdom

Peter O'Brien studied for a degree and PhD at the University of Cambridge, carrying out a PhD supervised by Stuart Warren. After the award of his PhD in 1995, he moved to the University of York as a Royal Commission for the Exhibition of 1851 Research Fellow. In March 1996, he was appointed as a lecturer in organic chemistry at the University of York and was promoted to Senior Lecturer (2002), Reader (2005) and Professor (2007). In recent years, he was awarded the Royal Society of Chemistry's Organic Stereochemistry Award (2013), a Vice-Chancellor's Teaching Award (2014-15) and the AstraZeneca, GlaxoSmithKline, Pfizer & Syngenta prize for Process Chemistry Research (2017). He is currently Chairman of the Royal Society of Chemistry's Heterocyclic and Synthesis Group. The O'Brien group's research focuses on contemporary organic synthesis.

Current research topics include the synthesis of nitrogen and oxygen heterocycles using organolithiums and the design, synthesis and biological screening of 3-D fragments.

EXPLORING 3-D PHARMACEUTICAL SPACE: NEW CH FUNCTIONALISATION REACTIONS OF OXYGEN AND SULFUR HETEROCYCLES

Peter O'Brien (1), Alice Kwong (1), Masakazu Atobe (1,2), Nico Seling (1), Kevin Kasten (1)

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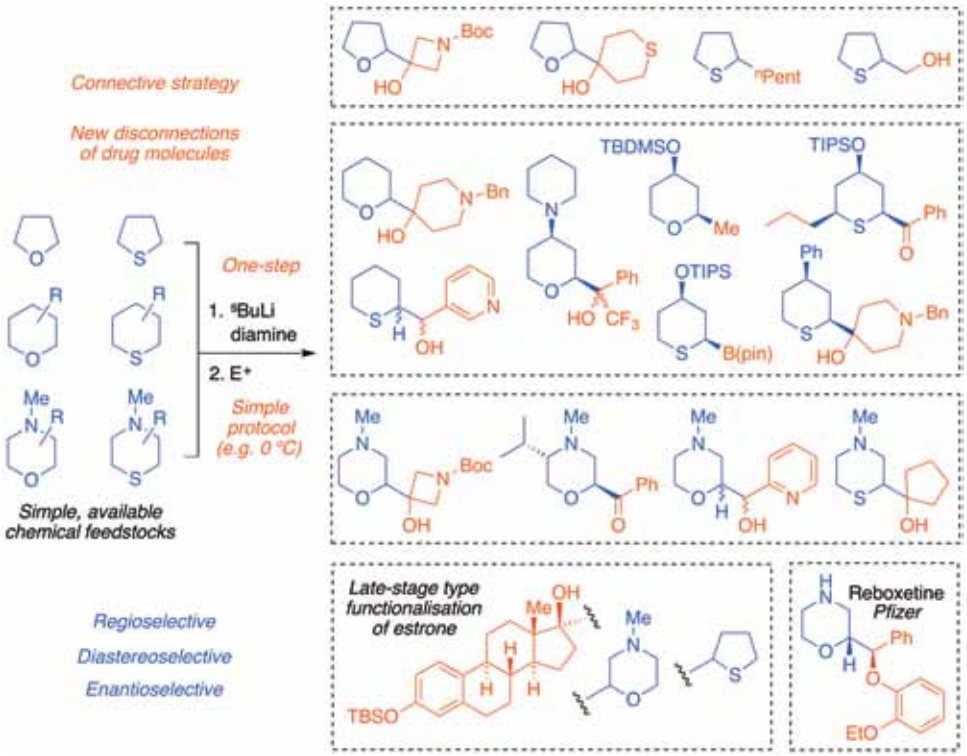
The development of de novo CH functionalisation reactions has transformed the landscape of organic synthesis, and has enabled new bond disconnections for medicinal chemistry applications. Deploying CH functionalisation within a late-stage manifold allows analogues to be rapidly prepared in drug discovery programmes. Despite these developments, methodology for sp^3-sp^3 cross coupling on cyclic substrates remains relatively rare.

The O'Brien group has a long-standing interest in the synthesis of pharmaceutically-relevant nitrogen heterocycles using lithiation-trapping.[1-4] We now report that simple and convenient lithiation protocols can be used to carry out the direct CH functionalisation of oxygen and sulfur heterocycles to generate a range of sp^3 -rich 3-D heterocyclic building blocks for use in medicinal chemistry (see scheme). Full details on the optimisation, mechanism, regioselectivity and diastereoselectivity of this new CH functionalisation process, together with scope, limitations and applications in late-stage functionalisation will be presented. This will include the first examples of the asymmetric lithiation-trapping of cyclic ethers.



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Peter DRAGOVICH

Genentech, United States

Peter Dragovich received a B.S. in chemistry from UC Berkeley and subsequently obtained a Ph.D. in synthetic organic chemistry from Caltech under the direction of Professor Andrew Myers. He has worked in the pharmaceutical industry for more than 20 years in both large-pharma and biotech organizations and has performed a variety of research and management activities during that time. He joined Genentech in 2010 and has since worked on multiple projects in both the immunology and oncology therapeutic areas. He is currently a Staff Scientist in the Discovery Chemistry Department and leads the company's efforts to identify novel payloads and linkers that can be utilized for the creation of new antibody-drug conjugates.

MECHANISM-BASED TOXICITIES ASSOCIATED WITH NAMPT INHIBITION AND RELATED MITIGATION STRATEGIES

Peter Dragovich

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Nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the rate-limiting event in the two-step conversion of nicotinamide (NAM) to the enzyme co-factor nicotinamide adenine dinucleotide (NAD) and thus plays a key role in maintaining NAD levels required for cell survival. Blocking NAMPT activity is therefore expected to impair the growth of tumor cells, which are often highly reliant on NAD-dependent processes, and this approach is currently viewed as a novel strategy for the development of new anticancer agents. However, non-cancerous cells that require robust NAD supplies may also rely on NAMPT activity for survival. To better define such dependencies, we profiled several structurally diverse and highly potent NAMPT inhibitors using multiple in vitro and in vivo toxicity assessments. These activities involved preclinical models of thrombocytopenia [colony forming unit-megakaryocytes (CFU-MK)] and the evaluation of rodent retinal and cardiac toxicity (including in vitro assessment of cardiomyocyte toxicity). A weakly-active structural isomer of one potent NAMPT inhibitor was included in these experiments as a negative control. These efforts demonstrated that the potent NAMPT inhibitors exhibited significant toxicities in all of the MK, retinal, and cardiac evaluations. Our work also indicated that the observed toxicities were on-target and were directly related to NAMPT inhibition. Efforts to mitigate these toxicities were subsequently made and included: (1) compound physiochemical property modifications to reduce retinal exposure and (2) co-administration of nicotinic acid (NA) which can enable NAD production through a NAMPT-independent pathway.

Douglas THOMSON

Cellzome, Germany

Douglas Thomson currently holds a position at Cellzome, A GSK Company in Heidelberg, Germany. He obtained his PhD in organic chemistry from the University of Strathclyde in Glasgow, UK and subsequently joined the High throughput Chemistry Department of BayerCropScience in Frankfurt, Germany as a PostDoc. Before joining Cellzome in 2011, Douglas was a medicinal chemist at the Institute of Cancer Research and Elara pharmaceuticals.

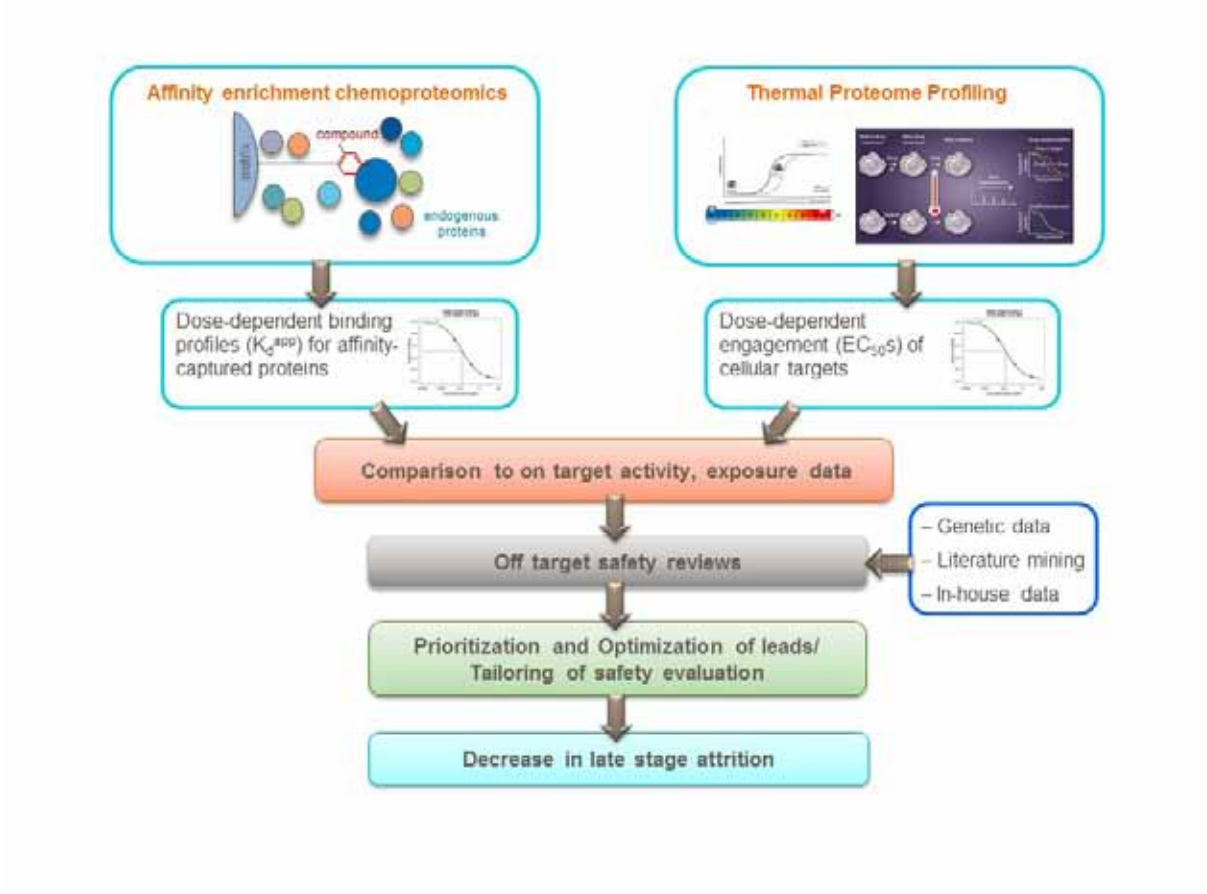
At Cellzome, the focus of his research is on the utilization of mass spec driven proteomics to determine a molecules off-target profile in the context of preclinical toxicology assessments.

UTILIZING IN DEPTH UNDERSTANDING OF A MOLECULES OFF-TARGET PROFILE TO TAILOR CLINICAL AND PRECLINICAL SAFETY ASSESSMENTS

Douglas Thomson

Cellzome A GSK Company, Heidelberg, Germany

One of the foremost challenges facing the pharmaceutical industry is the high attrition rate of drug candidates in phase II or III clinical trials. An analysis of the period 2013-2015, revealed that safety concerns accounted for approximately one quarter of all the late stage failures, with only a lack of efficacy the cause of more failures.[1] A contributing factor to safety related issues are adverse events caused by the molecules off-target activities. Therefore, an in depth understanding of a drug candidates selectivity profile already at the pre-clinical stage could prove to be valuable in the reduction of these clinical failures. It enables the early identification of potential liabilities and subsequently, the development of a strategy to monitor these. Therefore aiding with compound prioritization and optimization and ultimately assist in the selection of a molecule for progression with the greatest chance of success. At Cellzome, we utilize two complementary proteomics based approaches to determine the off-target profile of late leads. The first approach is Affinity enrichment chemoproteomics, using affinity matrices generated from functionalized analogues of the investigated compound.[2] The second approach is Thermal proteome profiling, which monitors compound induced changes in proteins thermal stability.[3] In this talk I will use relevant examples to outline this strategy and the technologies used.



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Andreas BRINK

F. Hoffmann-La-Roche, Switzerland

Andreas Brink works as a Principal Scientist/ Laboratory Head within Pharmaceutical Sciences focused on Drug Metabolism and High Resolution Mass Spectrometry. After his studies of chemistry and biology he received his Ph.D. in 2007 in the field of genetic toxicology at the Department of Toxicology and Pharmacology of the University Würzburg.

Since 10 years at F. Hoffmann-La Roche his responsibilities and interest developed into various aspects of drug metabolism throughout Drug Discovery and Development of different modalities (small molecules, peptides, oligonucleotides). The support of medicinal chemists to reduce the potential for reactive metabolite formation in lead optimization is one of his main tasks. Recently, his interest expanded to Mass Spectrometry Imaging and its application in pre-clinical research on drug toxicity, efficacy, metabolism and tissue distribution.

REDUCING BIOACTIVATION POTENTIAL OF DRUG CANDIDATES: IMPLICATIONS FOR PRECLINICAL DRUG OPTIMIZATION

Andreas Brink, Axel Pähler, Christoph Funk, Franz Schuler, Simone Schadt

Roche Pharma Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, 4070 Basel, Switzerland

The bioactivation of drugs to chemically reactive metabolites is an unwanted property. Cumulative evidence suggests that reactive metabolites play a causal role in several forms of drug-induced toxicities. In particular drug-induced idiosyncratic adverse drug reactions involving severe clinical symptoms such as hepatic injury are of great concern in the drug development and post approval stage. The underlying mechanisms are multifactorial and a general link between cause and effect with respect to bioactivation in humans with clinical outcome remains elusive. At present, there is no accepted *in vivo* model or follow-up method to assess whether compounds that form reactive metabolites will trigger idiosyncratic drug reactions in humans. Thus, the risk of drug candidates forming reactive metabolites is difficult to manage throughout preclinical and clinical development as the candidates could put patients at risk. Many pharmaceutical companies therefore aim to reduce reactive metabolite formation by chemical modification at early stages of drug discovery. A practice often applied is the detection of stable trapping products of electrophilic intermediates with nucleophilic trapping reagents to guide rational structure-based drug design while maintaining high potency, selectivity and favorable pharmacokinetic properties. This contribution delineates this strategy to minimize the potential for reactive metabolite formation of clinical candidates during preclinical drug optimization, exemplified by the experience at Roche over the last decade. For the majority of research programs it was possible to proceed with compounds optimized for reduced covalent binding potential. Such optimized candidates are expected to have a higher likelihood to succeed throughout the development processes and result in safer drugs.

Martin PETTERSSON

Pfizer, United States

Martin Pettersson received his BS in chemistry from Indiana University, Bloomington, in 1998 where he did undergraduate research in the laboratory of Professor David R. Williams. He then joined Pfizer as a medicinal chemistry research associate and contributed to projects in therapeutic areas such as inflammation, allergy & respiratory, and antibacterials. In 2002, he began his graduate studies at the University of Texas at Austin under the guidance of Professor Stephen F. Martin. After receiving his Ph.D. in 2007, he joined Pfizer Worldwide Research and Development as a medicinal chemist, and he is currently an Associate Research Fellow in the Internal Medicine chemistry group in Cambridge, MA. At Pfizer he has made significant contributions as a medicinal chemistry team leader for programs such as Gamma Secretase Modulators and Apolipoprotein E, and these efforts have led to a strong interest in property-based drug design.

He is actively involved in the area of phenotypic drug discovery including phenotypic screening hit triage, safety strategies, and de-convolution of mechanisms of action. Martin's research interests also include targeting RNA using small molecules, and he recently organized a symposium on this topic at the New York Academy of Sciences. He is a co-author of 33 publications and patents/patent applications.

SMALL STRUCTURAL CHANGES LEADING TO MAJOR IMPACT ON SAFETY: DEVELOPING SAFETY STRATEGIES IN MEDICINAL CHEMISTRY

Martin Pettersson, Ph.D.

Pfizer Worldwide Research & Development, Cambridge, MA, USA

The continued high level of compound attrition is one of the major challenges in bringing new, innovative medicines to patients. Significant progress has been made over the past two decades designing molecules with improved absorption, distribution, metabolism, and excretion (ADME). Likewise, advances have been made in our understanding of how certain structural features and physicochemical properties correlate with increased probability of adverse events *in vivo*. Nevertheless, safety-related findings remain a major cause of attrition in preclinical toxicology studies as well as in phase 1 clinical trials.

This presentation will focus on safety strategies in medicinal chemistry and highlight case studies emphasizing how minor structural changes can have major impact on safety. In particular, the Pfizer γ-secretase modulator program for Alzheimer's disease encountered acute in vivo toxicity in a particular series whereas two closely related matched molecular pairs were well tolerated at high exposures. These observations led to the development of an *in vivo* phenotypic safety strategy involving the use of the un-paced isolated heart Langendorff model. This approach enabled efficient and compound-sparing assessment cardiovascular safety, and it demonstrates that small structural changes can lead to vastly different outcome in *in vivo* toxicology studies.

Eva Maria MARTIN

Eli Lilly, Spain

Dr Eva Martin received a Doctorate in Organic Chemistry from the University of Salamanca in 2001. She acquired additional expertise in different synthetic methodologies with short-term assignments in the Organic Chemistry Department of the Universities of London, Warwick and Cologne. In May 2001 she joined Lilly Forschung in Hamburg as a medicinal chemist and in September 2002 she moved to Lilly Alcobendas in Spain.

During her career Dr Eva Martin has made important contributions to projects in oncology, cardiovascular and endocrine areas. With strong expertise in lead generation, her interests are fragment based drug design and the development and implementation of new technologies in drug discovery with the aim to deliver faster and better clinical candidates for the unmet medical needs.

ADAS (AFFINITY DIRECTED AUTOMATED SYNTHESIS): A NEW TECHNOLOGY TO ACCELERATE LEAD GENERATION

Eva Maria Martin

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Lead generation requires several iterative cycles of molecular design, synthesis, purification, testing and data analysis. Using conventional approaches, each learning cycle can take up to several weeks. One of the reasons for the long cycle-times is the lack of integration between all these processes.

In order increase the speed and efficiency of hit-to-lead exploration and drug discovery new paradigms are required. In this context, we have developed at Lilly a new platform called ADAS (Affinity Directed Automated Synthesis) that integrates automated synthesis, purification and testing by affinity selection mass spectrometry (ASMS) in fast iterative cycles. An evolutionary algorithm is used to optimize the ligand affinity of a virtual library of compounds, selecting the compounds to be synthetized in each cycle.

An introduction to ADAS and examples of its application to optimize ligand affinity will be presented.

Monika ERMANN

Evotec, United Kingdom

Monika is working as project leader in Discovery Chemistry at Evotec (UK). She obtained her education at the Technische Universität Wien (TU Vienna) and her PhD from the University of Liverpool. After joining Evotec in 2001, she has led medicinal chemistry teams on hit-to-lead, fragment-based and lead-optimization projects across a number of target classes and therapeutic areas.

Her current research projects have a strong focus on phenotypic drug discovery and target deconvolution.

A CHEMIST'S GUIDE TO MODERN PHENOTYPIC DRUG DISCOVERY

Monika Ermann (1), Tim James (1), Ina Sternberger (2), Stefan Müller (3)

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In recent years phenotypic drug discovery (PDD) has seen a renaissance across industry and academia, triggered by an influential and perhaps controversial publication [1] (followed by [2-3]), claiming it as superior strategy to discover first-in-class drugs.

The basis of this approach relies on unbiased screening assays that focus on the modulation of disease-linked phenotypes in a predictive cellular setting [4], often using complex assay systems (ideally patient derived primary or iPs-derived cells). These are considered more physiologically relevant compared to often reductionist assays centered on a specific protein. This clear link to the disease can positively affect the translation of preclinical findings to patients and offers the possibility to identify compounds acting through either unknown targets or molecular mechanism of action (MMOA).

In addition advances in cellular, imaging and 'omics profiling technologies combined with network and systems biology approaches make the phenotype no longer the black box that it once was. However, we as medicinal chemists still face unique challenges: including the selection of screening libraries, molecular phenotyping [5] as new way of hit triaging and target deconvolution.

Evotec has collected learnings in various phenotypic campaigns and has created a road map to progress phenotypic projects from screening to target deconvolution and validation. We will outline the available strategies for chemists to consider when designing and synthesizing tool compounds for target ID and present case studies for performing successful phenotypic drug discovery programs.

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Koen HEKKING

Mercachem-Syncom, The Netherlands

Dr Koen Hekking is a group leader in the medicinal chemistry department at Mercachem (The Netherlands). He obtained his PhD in natural product synthesis and catalysis at the Radboud University in Nijmegen under the supervision of Prof. Floris Rutjes. In 2006 he joined Mercachem as senior scientist, and has held a group leader position since 2008, supervising a variety of (medicinal) chemistry projects. For the past 3 years, he has been responsible for supervising Mercachem's innovation projects. These projects involve development of novel peptidomimetic scaffolds, as well as early stage medicinal chemistry projects with an emphasis on protein-protein interactions and kinases.

CDK8 INHIBITORS WITH PRE-ENGINEERD LONG RESIDENCE TIME, EXHIBITING EFFICACY IN TUMOR XENOGRAFT MODELS

Koen Hekking (1), Bas Aerts (1), Pauline van Meurs (1), Eddy Damen (1), Holger Weber (2), Frank Totzke (2), Jan Ehlert (2), Christophe Schächtele (2), Michael Kubbutat (2), Gerhard Müller (1)

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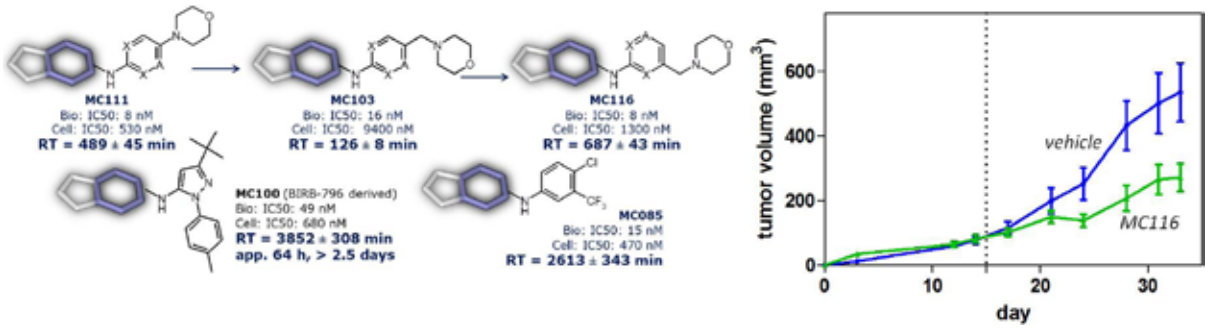
Upregulation of CDK8 has recently been described for colon cancer, gastric cancer, and melanoma, rendering CDK8 as an attractive target for the development of selective and efficacious anti-cancer drugs.

Based on the findings that CDK8 is amenable to a type II inhibition mode, we set out to design selective CDK8 inhibitors pursuing a privileged structure-based approach. The employed privileged structures are tailor-made for disrupting the hydrophobic R-spine within the N-terminal lobe of a kinase, thereby leading to an induced-fit mechanism of derived inhibitors that will exhibit a pre-engineered binding kinetic signature. This "Retro-Design" approach allows to keep the molecular complexity of inhibitors at a minimum level since the seed scaffold is targeted towards the deep pocket of the conformationally rearranged binding site.

Here we report on the discovery and optimization of a new class of CDK8 inhibitors. Frontrunner compounds exhibit excellent biochemical inhibition data and a high cellular efficacy in a variety of mechanism-of-action models as well as phenotypic models such as inhibition of anchorage-independent cell growth. The front-runner compounds show superior selectivity over a huge panel of kinases when compared to market approved drugs or to competitor CDK8 inhibitors. This selectivity is attributed to the distinct inhibition mechanism which is corroborated by detailed binding kinetic studies which reveal residence times in the range of several hours. Detailed structure-kinetic relationships will be discussed, as well as tumor growth inhibition in xenograft mouse models.



Sanne SCHRØDER GLAD

Nuevolution, Denmark

Dr Sanne Schrøder Glad is a principal scientist and project manager in Nuevolution and was part of the first pioneering team developing the Chemetics technology. She has been deeply involved in designing the libraries and building the compound collection at Nuevolution. Since 2010 she has been heading several lead discovery projects both in collaboration with big pharma companies and internal of which the RORγt program is the most progressed. Before joining Nuevolution, she was research scientist at Novozymes. She has a ph.d. in computational chemistry from University of Southern Denmark.

FROM MULTIPLE HIT SERIES TO (PRE)CLINICAL CANDIDATES USING DNA-ENCODED LIBRARY TECHNOLOGY

Sanne Glad

Nuevolution A/S, Rønnegade 8, DK-2100 Copenhagen Ø

DNA-encoded Library (DEL) technology is a powerful drug discovery technique. By combining tens of thousands of fragments in a split-and-mix fashion we create small-molecule libraries containing millions to trillions drug-like molecules. When screening these libraries against a target of choice, typically multiple chemical hit series ranging from low micromolar to picomolar affinity are identified. Often, these series are supported by instant and very comprehensive SAR information creating a unique starting point for a drug discovery project. Nuevolution is a pioneer within the field of DNA-encoded library technology and has successfully applied its DEL platform within both partnered and internal drug discovery projects. One of the most advanced internal projects is a RORγt inverse agonist project for applications within the field of inflammation.

The nuclear hormone receptor RORγt is a master regulator of IL-17A production. A small molecule targeting the ligand binding domain (LBD) of RORγt prevents production of IL-17A and may offer a convenient oral therapy for IL-17A-triggered inflammatory diseases. We have identified nanomolar potent small molecule inverse agonists directly from the screening of 830 million DNA-encoded compounds against the RORγt-LBD. The initial screening hits covered more than 15 diverse structural series with diverse property profiles. Hit-to-lead optimization using our optimization platform led to preclinical candidates with attractive DMPK properties, high oral bioavailability, strong in vivo efficacy across several anti-inflammatory animal models, and a benign safety profile.

During the screening phase, we also identified potent ROR t agonists, which led to a separate project. Using a different screening paradigm led to further enrichment of agonists with lead properties. One compound from this effort is now being evaluated for efficacy within oncology.

DEL technology has proven to be a powerful engine for lead generation. The significant advantage of typically having multiple hit series and significant SAR directly from screening provides the project team with a unique starting point for subsequent hit-to-lead optimization.

Kai JOHNSSON

Max Planck Institute for Medical Research, Germany

Kai Johnsson is Director at the Max Planck Institute for Medical Research, Department of Chemical Biology since 2017. His current research interests focus on the development of chemical approaches to visualize and manipulate biochemical activities in living cells.

His past achievements include the introduction of methods to specifically label proteins in living cells (i.e. SNAP-tag and CLIP-tag), the development of new fluorescent probes and sensors as well as the characterization of mechanism of actions of drugs and drug candidates.

Kai Johnsson is Associate Editor of ACS Chemical Biology since 2005 and member of the Editorial Advisory Board of Science. He is co-founder of Covalys Biosciences, Spirochrome, Quartet Medicines and Lucentix.

FLUORESCENT AND BIOLUMINESCENT SENSOR PROTEINS

Kai Johnsson

Max-Planck Institute for Medical Research, Department of Chemical Biology, 69120 Heidelberg, Germany; E-mail: kai.johnsson@mpimf-heidelberg.mpg.de

The topic of my presentation will be how a combination of protein engineering and synthetic chemistry can be exploited to generate fluorescent and bioluminescent probes for live-cell imaging.

Specifcally, I will talk about our attempts to introduce a new class of fluorescent sensor proteins that permit to visualize drug and metabolite concentrations in living cells with high spatial and temporal resolution. I will also discuss how these sensor proteins can be utilized for point-of-care therapeutic drug monitoring.

Gonçalo BERNARDES

Instituto de Medicina Molecular, Portugal
University of Cambridge, United Kingdom

Dr Gonçalo Bernardes is a Group Leader at the Department of Chemistry, University of Cambridge, U.K.. He is also the Director of the Chemical Biology and Pharmaceutical Biotechnology Unit at the Instituto de Medicina Molecular, Portugal. After completing his D.Phil. degree in 2008 at the University of Oxford, U.K., he undertook postdoctoral work at the Max-Planck Institute of Colloids and Interfaces, Germany, and the ETH Zürich, Switzerland, and worked as a Group Leader at Alfama Lda in Portugal. He started his independent research career in 2013, and his research group interests focus on the development of site-selective chemical protein modification for basic biology and drug development.

He is a Royal Society University Research Fellow and the awardee of a Starting Grant from the European Research Council (TagIt).

CHEMICAL PHYSIOLOGY OF ANTIBODY CONJUGATES AND NATURAL PRODUCTS

Gonçalo Bernardes (1,2)

1) University of Cambridge, Department of Chemistry, Lensfield Road, Cambridge CB2 1EW, UK
2) Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal

Our research uses chemistry principles to address questions of importance in life sciences and molecular medicine. This lecture will cover recent examples of emerging areas in our group in:

(i) methods developed for site-selective chemical modification of proteins/antibodies at cysteine, disulfide and lysine and their use to build stable and functional protein/antibody conjugates for *in vivo* applications [1,2];

(ii) harnessing the power of natural product architectures in cancer chemical biology. By identifying on- and off-targets for anti-cancer entities and unveiling the underlying molecular mechanisms of target recognition, we explore the use of natural products as cancer modulators and ligands for the selective delivery of cytotoxic payloads [3]. In one example, we have validated a natural product as a potent, ligand efficient, allosteric modulator of 5-lipoxygenase (5-LO). We found an unprecedented link between the anticancer activity of the molecule and engagement of 5-LO in blood cancer cells in vitro; and demonstrated the ligand-target association by confirming efficacy of the molecule in a disease mouse model of systemically disseminated, drug-resistant acute myeloid leukemia (AML).

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Benjamin CRAVATT

The SCRIPPS Research Institute, United States

Dr Cravatt is currently a Professor and the Norton B. Gilula Chair of Chemical Biology in the Department of Molecular Medicine at the Scripps Research Institute. He earned his B.S. in biological sciences and a B.A. in history from Stanford University and his Ph.D. in macromolecular and cellular structure and chemistry from The Scripps Research Institute.

His research has won a number of awards, including the Eli Lilly Award in Biological Chemistry from the American Chemical Society, the Merck Award from the American Society for Biochemistry and Molecular Biology, and election into the National Academy of Sciences and National Academy of Medicine.

ACTIVITY-BASED PROTEOMICS – PROTEIN AND LIGAND DISCOVERY ON A GLOBAL SCALE

Benjamin Cravatt

The Scripps Research Institute, Department of Chemical Physiology, The Skaggs Institute for Chemical Biology, 10550 North Torrey Pines Road, CA 92037 La Jolla, United States

Genome sequencing projects have revealed that eukaryotic and prokaryotic organisms universally possess a huge number of uncharacterized proteins. The functional annotation of these proteins should enrich our knowledge of the biochemical pathways that support human physiology and disease, as well as lead to the discovery of new therapeutic targets. To address these problems, we have introduced chemical proteomic technologies that globally profile the functional state of proteins in native biological systems. Prominent among these methods is activity-based protein profiling (ABPP), which utilizes chemical probes to map the activity state of large numbers of proteins in parallel. In this lecture, I will describe the application of ABPP to discover and functionally annotate proteins in mammalian physiology and disease. I will also discuss the generation and implementation of advanced ABPP platforms for proteome-wide ligand discovery.

David TELLERS

MSD, United States

Dr David Tellers received his PhD from Berkeley under the guidance of Professor Robert G. Bergman. In 2001, he joined Merck working in both the Department of Chemical Engineering and Process Research where he focused on route development, catalysis, and automation. He made contributions to multiple programs, including Emend ™, Januvia ™, Cordaptive ™, and Vaniprevir ™. In 2008, he transferred to the Department of Medicinal Chemistry where he has had the opportunity to lead groups focused on oligonucleotide and peptide therapeutic development, early and late stage neuroscience and infectious disease programs, and chemical biology.

He is a Director in the Discovery Chemistry Modalities Group and currently leads the recruiting efforts for Medicinal Chemistry.

INTRACELLULAR DELIVERY OF MACROMOLECULES

David Tellers

Merck & Co. Inc (MSD)
770 Sumneytown Pike WP39-345 - 19486 West Point
United States

Alternative modalities, those between small molecules and biologics, offer a unique opportunity for intracellular applications. Delivering these molecules across the cellular membrane continues to be a central challenge. This talk will highlight advances in the chemistry and characterization of oligonucleotides and peptides for transmembrane delivery.

Eric VALEUR

AstraZeneca, Sweden

Eric Valeur obtained his PhD from the University of Edinburgh (Prof. Mark Bradley) and then joined the Northern Institute for Cancer Research in Newcastle working as Postdoctoral Fellow on inhibitors of MDM2-p53 in Prof. Roger Griffin's group. Subsequently, he led medicinal chemistry teams first at Merck-Serono in Paris and then at Novartis in Basel. In particular, he was involved in the development of non-peptidic proteases inhibitors within the Expertise Protease Platform. In 2014, he joined AstraZeneca in Sweden, as Associate Director for New Modalities Medicinal Chemistry.

His vision is to integrate chemical spaces, in essence leveraging the potential of each modality either separately or as hybrids. He also established and steers a unique approach to innovation consisting of a Satellite Unit based at the Max Planck Institute in Dortmund, Germany, with three AstraZeneca scientists being directly embedded within Prof. Herbert Waldmann's research group.

NEW MODALITIES PROBE AND HIT FINDING FOR CHALLENGING TARGETS IN CARDIOVASCULAR AND METABOLIC DISEASES

Eric Valeur

Medicinal Chemistry, Cardiovascular and Metabolic Diseases, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden

The development of genomics and biomarkers, together with better access to human tissue samples, have strengthened the genetic relationships between diseases and selected biological targets. However, these targets with strong human validation are increasingly challenging, and include E3 ligases, transcription factors and more generally protein-protein and protein-nucleic acid interactions. Novel approaches to access different and novel chemical modalities are required to address these target classes since small molecules are typically less suited for the large interfaces involved. These different molecules, or 'New Modalities', provide medicinal chemists with the opportunity to branch out from their classical skills set to address 'undruggable' therapeutic targets in the most appropriate way. However, many challenges are faced with the identification and development of 'New Modalities' including hit finding, cell penetration and tissue access, to mention a few.

The presentation will highlight how hit finding of New Modalities can be approached in the context of cardiovascular and metabolic diseases. In the field of next generation peptides, a novel strategy consists in screening genetically encoded cyclic peptide libraries directly in bacterial cells, linking inhibition of a target to cell survival. With this approach a tool peptide against IDOL, an E3 ligase involved in the degradation of the LDL receptor and a regulator of blood cholesterol levels, could be identified and enabled the discovery of novel biological cross-talks around IDOL.

Another alternative is to mimic protein epitopes to pursue structure-based drug design. In this respect, an underexploited class of macrocycles, namely peptide-small molecule hybrids, will be presented in the context of hit finding to cyclise protein 'hot loops'.

Kerry BENENATO

Moderna Therapeutics, United States

Kerry received her B.S. in Chemistry from Providence College after which she moved to Boston College, where she obtained her Ph.D., working in the labs of Amir Hoveyda, focusing on Cu-catalyzed enantioselective allylic substitution reactions. Following that she worked in the labs of Matt Shair at Harvard University as a NIH postdoctoral fellow. After her post-doc she joined Astra Zeneca Pharmaceuticals, where she worked in the Department of Infectious Diseases, focusing on the identification of new therapies for Gram-negative infections. After seven years at AZ, she moved to Moderna Therapeutics, where she currently leads the department of Delivery Chemistry, focusing on the development of novel delivery vehicles for mRNA-based therapeutics.

MESSENGER RNA AS A NOVEL THERAPEUTIC APPROACH

Kerry Benenato

Moderna Therapeutics, 200 Technology Square, MA 02139 Cambridge, United States

The challenge of developing mRNA as a therapeutic is due to several factors. To start, mRNA requires a delivery vehicle which must be able to protect the mRNA from degradation, shield the mRNA from the immune system and release its cargo in a tissue and cell specific manner. Once delivered intracellularly, the mRNA must efficiently engage the ribosome without triggering immune sensors like the TLRs and RIG-I. We have found parallel optimization of the mRNA chemistry and the lipid nanoparticle delivery vehicle is integral to the solution to each challenge. This effort has resulted in a drug product which affords high level of protein expression with an optimized pharmacokinetics and a clean tolerability profile. This presentation will discuss some of the most important structure activity relationships of the mRNA and the lipid nanoparticle chemistry.

Niall ANDERSON

GlaxoSmithKline, United Kingdom

Niall received his masters degree in medicinal chemistry from the University of Strathclyde and subsequently joined GlaxoSmithKline's Discovery Chemistry group in Stevenage, England in 2006. From there, Niall gained experience across multiple phases of drug discovery throughout GSK from hit identification to late stage lead optimisation. In 2014 Niall gained his PhD in a collaborative programme between GSK and the University of Strathclyde on a project entitled "The design, synthesis and optimisation $\alpha v\beta 6$ antagonists as potential idiopathic pulmonary fibrosis agents".

Currently Niall is working in the Protein Degradation Discovery Performance Unit where he is looking to utilise PROTAC technology to design medicines of the future.

PROTEOLYSIS TARGETTING CHIMERA: A NEW FRONTIER IN MEDICINAL CHEMISTRY

Niall Anderson

Protein Degradation DPU, GlaxoSmithKline, Gunnelswood Road, Stevenage, SG12NY, England

The concept of targeting a specific protein for degradation through hijacking the body's own ubiquitin proteosome system represents a truly exciting new frontier in medicinal chemistry and opens the door for a completely novel class of medicines to evolve.[1]

Proteolysis targeting chimera (PROTACs) are heterobifunctional small molecules which simultaneously bind both a target protein and an E3 ligase.[2] When the target protein and E3 ligase are brought into close proximity by the PROTAC, the protein is tagged with ubiquitin, ultimately resulting in its degradation by the proteosome (Figure 1). This novel approach offers multiple potential advantages when compared to small molecule inhibitors, including reduced dose and extended duration of action.[3]

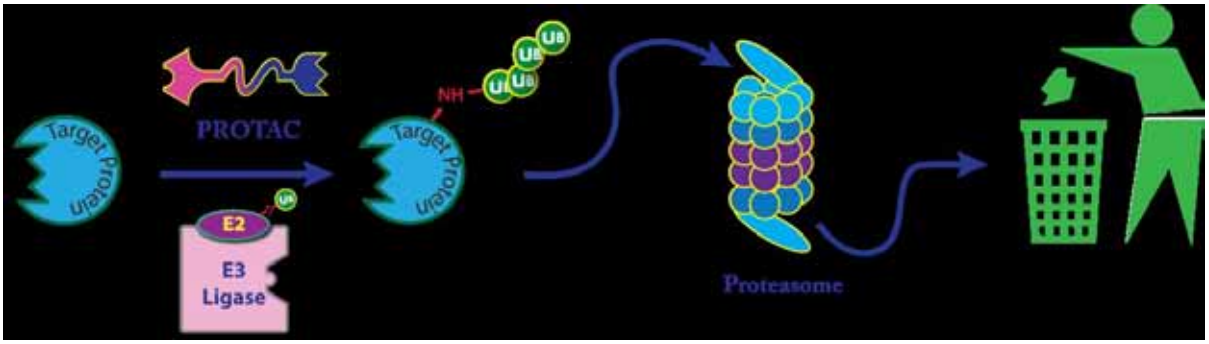

Figure 1: General mechanism of action of PROTACs

Recent developments in the field of protein degradation have mainly focussed on a relatively small number of intracellular targets, including kinases[4] and bromodomains.[5] This talk will focus on the key question of target scope and the novel strategies being undertaken within the Protein Degradation DPU to address this issue and take advantage of this rapidly evolving field.

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Matthew GAUNT

University of Cambridge, United Kingdom

Matthew Gaunt graduated from the University of Birmingham with 1st Class Honours for Chemistry in 1995. He moved to the University of Cambridge to carry out his graduate studies as a Wellcome Trust Scholar with Dr. Jonathan B. Spencer, finishing in 1999. Following this he was awarded a prestigious GlaxoWellcome Postdoctoral Fellowship that he took to the University of Pennsylvania to work with Professor Amos B. Smith. He returned to the UK in 2001 to work with Professor Steven Ley as a Junior Research Fellow at Magdalene College, and was also awarded a Ramsay Memorial Fellowship. He began his independent research career in October 2003 at the University of Cambridge and was awarded a Royal Society University Research Fellow in October 2004. In October 2006 he was appointed Lecturer in Organic Chemistry, and a Philip & Patricia Brown Next Generation Fellow at the University of Cambridge. In October 2010 he was promoted to Reader in Chemical Synthesis. In October 2012 he was promoted to Professor.

Matthew recently joined the Editorial Board of the RSC journal, Chemical Science, as Associate Editor and is a member of the Scientific Advisory Board of Advanced Synthesis and Catalysis. The Group's research interests are focused on the invention of catalytic strategies for chemical synthesis and the development of cascade processes for the rapid assembly of natural products.

NEW CHEMICAL TOOLS FOR THE LATE STAGE FUNCTIONALIZATION OF BIOMOLECULES

Matthew Gaunt

University of Cambridge, Department of Chemistry
Lensfield Road, CB2 1EW Cambridge, United Kingdom

Nature displays a remarkable ability to carry out site-selective post-translational modification of proteins, therefore enabling a dramatic increase in their functional diversity. Inspired by this, chemical tools have evolved for the synthetic manipulation of protein structure and function, and have become essential to the continued advancement of chemical biology, molecular biology and medicine. However, the number of chemical transformations suitable for effective protein functionalization is limited because the stringent demands inherent to biological systems preclude the applicability of many potential processes[2]. Put simply, these chemical transformations often need to be selective at a single site on a protein, proceed with very fast reaction rates, operate under biologically ambient conditions and should provide homogeneous products with near perfect conversion. While many elegant bioconjugation methods exist at cysteine, lysine and tyrosine, we reasoned that a method targeting a less explored amino acid would significantly expand the protein functionalization toolbox. Herein, we report the development of a multifaceted-approach to protein functionalization based on chemoselective labelling at methionine residues. By exploiting the unique electrophilic reactivity of a bespoke hypervalent iodine reagent, one can target the *S*-Me group in the side-chain of methionine. The bioconjugation reaction is fast, selective, and operates at low μM concentrations, displays broad substrate scope and is complementary to existing bioconjugation strategies. Moreover, the new reaction produces a protein conjugate that is, itself, a high energy intermediate with reactive properties that can serve as a platform for the development of secondary, visible-light mediated bioorthogonal protein functionalization processes. Taken together, we believe that these approaches will conveniently deliver versatile protein conjugates, which could be useful for probing biological systems.

Nicolai CRAMER

Ecole Polytechnique Fédérale de Lausanne, Switzerland

Nicolai Cramer obtained his PhD from the University of Stuttgart under the guidance of Sabine Laschat in 2005. After postdoctoral studies with Barry Trost at Stanford as a Feodor-Lynen scholar, he started in 2007 his independent career as Habilitant associated to the chair of Erick Carreira at the ETH Zurich. He received the venia legendi in 2010 and subsequently moved to EPFL as Assistant Professor. Nicolai was promoted to Associate Professor in 2013 and subsequently to Full Professor in 2015.

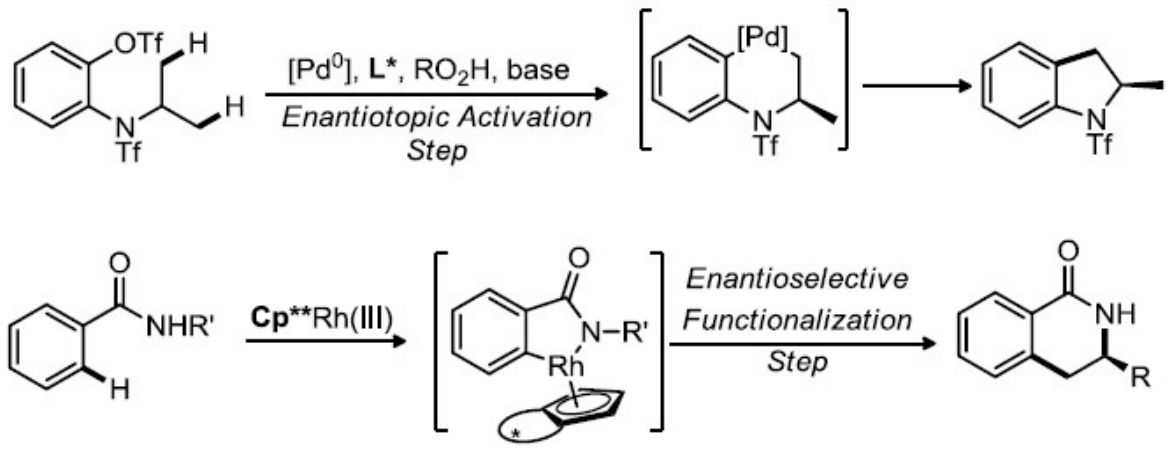
His research interests encompass enantioselective metal-catalyzed transformations and their implementation for the synthesis of biologically active molecules. A key focus of his research is the development of asymmetric C-H bond functionalizations and the design of broadly useful chiral ligands.

THE QUEST FOR EFFICIENT LIGANDS IN ASYMMETRIC C-H FUNCTIONALIZATIONS

Nicolai Cramer

Laboratory of Asymmetric Catalysis and Synthesis, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

Reactions involving the selective activation and subsequent functionalization of C-H bonds have a high synthetic potential because of their economic and ecological benefits. Despite significant progress in addressing reactivity and selectivity issues, as well as refining mechanistic understanding of the different pathways, catalytic enantioselective transformations remain largely underdeveloped. Often harsh conditions, the use of uncommon ligand systems or bar metal salts as catalysts have hampered developments in this area. Therefore, the design and development of efficient ligand systems is critical to the success these transformations. The presentation will focus on our recent developments of activating enantiotopic C(sp^3)-H bonds using Pd(0)-catalysts.[1-4] The utility and versatility of chiral cyclopentadienyls as enabling ligands for a variety of late transition-metals for enantioselective C-H activations will be discussed, showcasing the use of these techniques for a streamlined access to relevant small molecules.[5-7]



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Darren J. DIXON

University of Oxford, United Kingdom

Darren J. Dixon is Professor of Chemistry at the University of Oxford. He obtained his BA, MA and D. Phil (supervised by Professor Stephen Davies) from the University of Oxford. After a postdoctoral appointment with Professor Steve Ley FRS he was appointed to the Staff of the Department of Chemistry, University of Cambridge in 2000. In 2004 he took a Senior Lectureship at The University of Manchester and was promoted to Reader in 2007. In 2008, he moved to his current position at Oxford where he is also the Knowles-Williams Tutorial Fellow in Organic Chemistry at Wadham College and the Director of the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine.

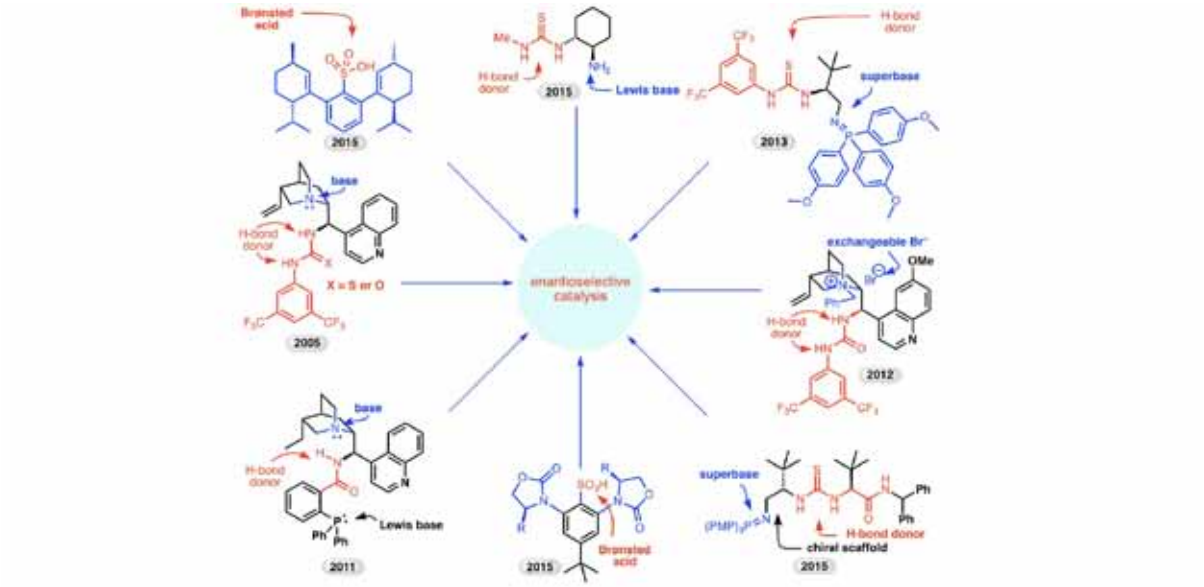
His research is centered on the development of new catalyst-enabled synthetic methodologies and their application to the synthesis of structurally complex scaffolds, natural products and molecules of biological significance. His honors include an EPSRC Leadership Fellowship, the RSC Catalysis in Organic Chemistry Award, the AstraZeneca Research Award and Novartis Chemistry Lectureship.

CATALYTIC APPROACHES TO SIMPLIFYING SYNTHESIS

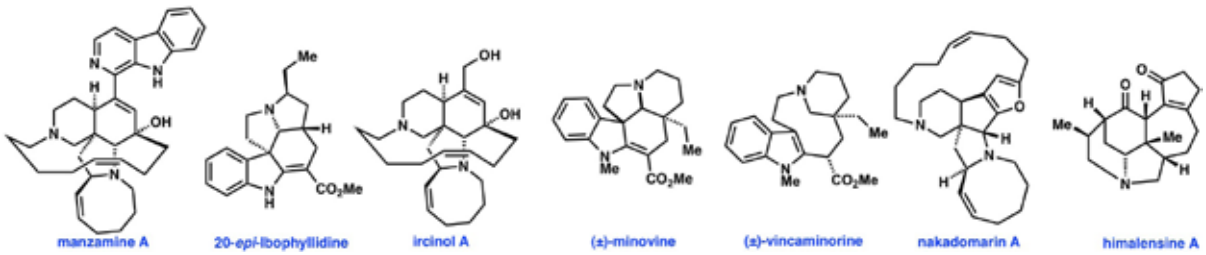
Darren James Dixon

Department of Chemistry, University of Oxford, Oxford, OX1 3TA, UK.

Catalysts that provide new reactivity and stereocontrol in efficient bond-forming reactions, are essential tools for converting low cost starting materials into high value, structurally complex, stereochemically defined product materials. In this presentation, new families of metal-free and metal-rich cooperative catalysts and their use in highly enantioselective C-C bond forming reactions and other relevant transformations, will be described.



Their strategic application to the discovery of new one-pot reaction cascade processes to generate novel, stereochemically defined scaffolds and architectures useful for library and target synthesis will also be discussed. Further application of selected methodologies as pivotal carbon-carbon bond forming steps in the total synthesis of a range of manzamine, aspidosperma, iboga, strychnos and daphniphyllum alkaloids will then be discussed. These syntheses serve to illustrate how complex molecular targets can be rapidly accessed when combinations of catalyst-controlled reactions, one-pot multistep procedures and powerful route-shortening cascades are designed into the overall synthetic sequence.



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Mark LAUTENS

University of Toronto, Canada

Mark Lautens attended the University of Guelph (B.Sc.) followed by his Ph.D. in 1985 with Barry M. Trost at the University of Wisconsin-Madison. He conducted postdoctoral studies with David A. Evans at Harvard University. He joined the faculty at the University of Toronto in 1987 and is currently University Professor, J.B. Jones Distinguished Professor and AstraZeneca Endowed Chair of Organic Synthesis. From 20013-2013 he was an NSERC/Merck Frosst Industrial Research Chair.

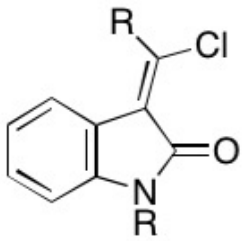
Among his awards are the E.W.R. Steacie Fellowship, KIllam Fellowship, CIC Medal, A.P. Sloan Fellow, A.C. Cope Award, Fellowship in the Royal Society of Canada, Alexander von Humboldt Awardee and Pedler Award from the Royal Society of Chemistry (UK). IN 2016, was invested as Officer of the Order of Canada. His research areas are in discovery and applications of novel catalytic reactions and strategies for the synthesis of bioactive molecules of interest to the pharmaceutical industry.

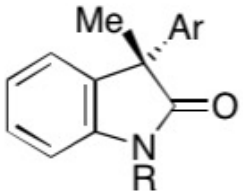
SYNTHETIC ROUTES TO OXINDOLES VIA METAL CATALYSIS

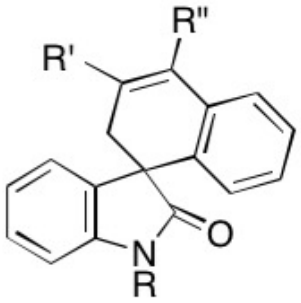
Mark Lautens

Davenport Laboratories, Department of Chemistry, University of Toronto, Toronto, ON Canada M5R 3H6

We have recently been developing new approaches to oxindoles via three classes of reactions. We have examined the reversible oxidative addition as an straightforward entry into halogenated methylene oxindoles and found high stereoselectivity.[1] Reductive arylation catalyzed by rhodium has also provides related scaffolds in high enantioselectivity.[2] In addition, we have examined a cyclization-C-H activation-insertion approach to spirooxindoles.[3] Recent advances on these approaches will be presented.







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Tom HEIGHTMAN

Astex Pharmaceuticals, United Kingdom

Tom Heightman studied Chemistry at Oxford, and gained his PhD at the ETH in Zurich. In 1998, he joined GlaxoSmithKline in Harlow, UK, where he held positions of increasing responsibility, becoming head of lead discovery for GSK's Neurology CEDD 2006-2008. During this time he made significant scientific and leadership contributions to the discovery of over a dozen preclinical candidates across multiple therapeutic areas, of which 4 so far have reached phase II proof of concept studies. In 2008, he joined the SGC at Oxford University, as a co-founding PI and project manager for the SGC's Epigenetics Chemical Probes Consortium, overseeing the creation of platforms for bromodomain and demethylase inhibitor discovery. Since January 2011, Tom has worked at Astex in Cambridge, UK, where he is currently VP & Head of Chemistry.

Tom is a fellow of the Royal Society of Chemistry, having served on the Biological and Medicinal Chemistry Sector committee and the Chemistry-Biology Interface Division Council, and has authored more than 90 publications and patents.

DRUG DISCOVERY FOR CHALLENGING TARGETS BY X-RAY CRYSTALLOGRAPHIC FRAGMENT SCREENING

Tom Heightman

Astex Pharmaceuticals, Cambridge, UK

Fragment based drug discovery at Astex uses X-ray crystallographic and biophysical screening to detect the binding of small molecular fragments. Although such fragments bind with weak affinities, their small size allows them to bind with well aligned orientations that maximize their interaction with the target protein. Careful selection of fragment hits with vectors suitable for growing and optimization, supported by fast iterative structure-based design, allows potent inhibitors to be constructed with a highly complementary structure to the target protein.

The approach allows molecular weight and lipophilicity to be strictly controlled, providing leads with high ligand efficiency, which is of particular importance when addressing challenging targets with dispersed pharmacophores such as protein-protein interactions.

This talk will describe key aspects of fragment based drug discovery at Astex, illustrated by recent projects which successfully progressed from crystallographic fragment screens into pre-clinical and clinical drug candidates.

Rod HUBBARD

University of York & Vernalis, United Kingdom

Professor Rod Hubbard has been an academic at York for over 35 years working with methods for analysis and exploitation of protein structure. He developed molecular graphics and modelling methods in the 1980s and helped build Structural Biology at York during the 1980s and 1990s. He worked on the structure of many proteins of therapeutic importance combined with studies of protein-ligand interactions and methods in structure-based design. In 1997, he was a founding SAB member of what became Vernalis. Since 2001 he has split his time between Vernalis (fragment and structure based drug discovery) and York (fragment methods for chemical biology and industrial biotechnology).

In addition, he works with UK Research Councils and consults with pharmaceutical and technology companies around the world.

THE IMPACT OF FRAGMENTS ON DRUG DISCOVERY

Roderick Hubbard (1,2)

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Fragment-based lead discovery (FBLD) is now firmly established as a mature collection of approaches for the discovery of small molecules that bind to proteins[1]. The approach is being successfully applied in the search for new drugs, with many compounds now in clinical trials[2] and with the first fragment-derived compounds now treating patients[3,4]. The approach has also had a number of other impacts such as providing starting points for lead discovery for challenging, unconventional targets such as protein-protein interactions[3,5], increasing the use of biophysics to characterise compound binding and providing small groups, particularly in academia, with access to the tools to identify chemical probes of biological systems[6,7].

The central feature of FBLD is that the drug discovery process begins with identification (usually by biophysical methods) of small (below 250 MW), weakly binding (affinity of 100s of μM) compounds which are then optimised to drug candidates by structure-guided design. The advantages are that a small library can sample a potentially large chemical diversity to generate multiple novel lead series of compounds and that hits can be identified for new classes of target for which existing compound collections cannot provide a hit.

In this talk, I will start with a brief summary of the current methods and practises in FBLD illustrated with a few examples. I will then overview some of the recent developments and ideas – first for conventional targets (integrating fragments with HTS and some comments on chemical space and novelty) and then for non-conventional targets (protein-protein interactions, using surrogates for tough targets[8]). I will conclude with some comments on how the development of fragment methods has had an impact on drug discovery.

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Jean-François GUICHOU

CNRS, France

Jean-François Guichou graduated from the ENSCM « Ecole Nationale Supérieure de Chimie de Montpellier » in 1997. He moved to the University of Lausanne to carry out is PhD thesis under the supervision of Pr. Manfred Mutter, finishing in 2002. Following this he was awarded a Postdoctoral Fellowship in the CBS "Centre of Structural Biochemistry" to work with Dr Michel Kochoyan. In September 2005 he was recruited as Assistant Professor in Structural biology at the University of Montpellier. In September 2016 he was promoted to Professor in Structure based Drug Design. Jean-François is the co-founder of the start-up AGVdiscovery in March 2013 which developed targeted therapy in oncology (http://www.agv-discovery.com).

Jean-François is an expert in the field of human cyclophilin inhibitors.

The group research interests are focused on the development of new strategy for fragment screening and to discover new chemical entities for different applications: oncology, virology and infectious diseases.

RATIONAL DESIGN OF SMALL-MOLECULES INHIBITORS OF HUMAN CYCLOPHILINS WITH A PAN VIRAL ACTIVITIES BY FRAGMENT BASED DRUG DESIGN USING A LINKING STRATEGY

Lionel Colliandre (1), Abdelhakim Ahmed-Belkacem (2), Gelin Muriel (1), Bessin Yannick (1), Pawlotsky Jean-Michel (2), Guichou Jean-Francois (1)

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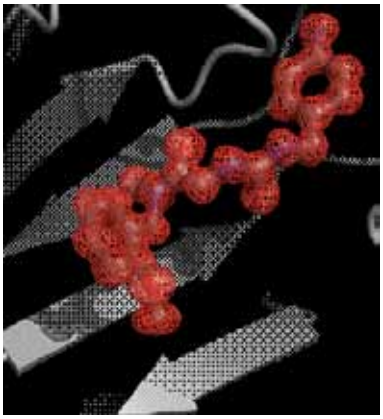
2) IMRB, Inserm U955, Equipe 18, Hôpital Henri Mondor, 94010 Créteil, France



The hepatitis C virus (HCV) is the leading cause of chronic hepatitis, of liver cirrhosis and hepatocellular carcinoma. Roughly 200 millions individuals are infected in the whole world and the infection by HCV causes approximately 280.000 deaths per year. The study of the complex of replication made it possible to highlight the crucial role of cellular partners, in particular the cyclophilins[1], in the driving process with the synthesis of new viral genomes and inhibition of these enzymes lead to new anti-viral agents. The Cyclophilins are enzymes that have been observed abundantly and ubiquitously in a wide range of tissue types and organisms[2,3]. They are characterized by the ability to catalyse the *cis-trans* isomerisation of peptidylprolyl bonds[4] (PPIases) which was identified as the rate-limiting step in protein folding. To design news Cyps inhibitors with low molecular mass, we applied a fragment-based screening approach on Cyclophilin D (CypD). We used X-ray crystallography and NMR that are well adapted to identify weak affinity fragments (mM). We solved 14 crystallographic structures of CypD in complex with fragments (2,00 - 0,97Å). Based on the fragments binding modes, we designed and optimized a new Cyps inhibitors family (proline mimetic). Our lead compound have an IC_{50} of 0,05µM on Cyp *in vitro* and have activities on differents virus (HCV, HIV and coronavirus) on replication *in cellulo*. The presentation will show the used of X-ray crystallography for the discovery of news human Cyps inhibitors using fragment based drug design using a linking strategy[5].

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Christoph GAUL

Novartis, Switzerland

Christoph Gaul, born and raised in Munich (Germany), studied chemistry at the LMU Munich (B.A. in chemistry), The University of Texas at Austin (M.A. in chemistry, Stephen Martin) and the ETH Zürich (Ph.D. in chemistry, Dieter Seebach), before he went on to conduct postdoctoral research at the Memorial Sloan Kettering Cancer Center New York (Sam Danishefsky). More than 10 years ago, Christoph started a career as a medicinal chemist at Novartis Switzerland, first in the Hit to lead group and later as a project and group leader in the oncology chemistry area. Currently, Christoph is heading the Hit Generation Sciences group at Novartis, building and providing expertise in hit generation chemistry and technology (e.g. DNA-encoded libraries).

FRAGMENT-CENTRIC METHODOLOGIES FOR THE DISCOVERY OF DOT1L INHIBITORS

Christoph Gaul (1), Frederic Stauffer (1), Henrik Möbitz (1), Clemens Scheufler (1), Rainer Machauer (1), Philipp Holzer (1), Cesar Fernandez (1), Ulrich Hommel (1), Ralph Tiedt (1), Andreas Weiss (1), Kim Beyer (1), Hugh Zhu (2)

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2) Novartis Institutes for Biomedical Research, Shanghai, China

Dot1L is the only known enzyme to methylate lysine 79 of histone 3 (H3K79), with the H3K79me2 mark being associated with active transcription. Under physiological conditions, Dot1L is critical for normal hematopoiesis, however, misdirected catalytic activity (methyltransferase) is believed to be causative for certain acute leukemias. Several oncogenic fusion proteins including MLL-ENL, MLL-AF4 and MLL-AF9 aberrantly recruit Dot1L to ectopic loci, leading to local hypermethylation of H3K79 and misexpression of genes (including HoxA9) which drive the leukemic phenotype. Inhibition of the methyltransferase activity of Dot1L in MLL-rearranged leukemias (mixed lineage leukemia, MLL) is predicted to reverse ectopic H3K79 methylation, leading to repression of leukemogenic genes (HoxA9, Meis1) and tumor growth inhibition.

Herein, we will describe our Dot1L hit finding strategy, including biochemical, biophysical and virtual approaches, and our medicinal chemistry strategy, strongly influenced by structure-based design and property-based optimization. Among other concepts, a fragment growing and linking approach as well as a fragmentation method will be discussed, leading to the discovery of structurally completely novel (non-SAM like), orally bioavailable Dot1L inhibitors with excellent cellular activity.

Jean QUANCARD

Novartis, Switzerland

Jean Quancard studied Chemistry at Ecole Normale Superieure in Paris and continued with a PhD in Chemical Biology at University of Pierre et Marie Curie. In 2004, he moved to Stanford University in the US for a Postdoc with Pr. Barry Trost.

Jean joined Novartis in 2006 in the Global Discovery Chemistry Department and since then worked in several therapeutic areas such as autoimmunity, oncology, ophthalmology and neuroscience. He also spent a few years in the protease platform, the expertise group focused on the discovery of protease inhibitors. Currently, he is Director and Head of Chemistry for the Musculoskeletal disease area.

DISCOVERY OF ALLOSTERIC MALT1 PROTEASE INHIBITORS WITH HIGH IN VIVO EFFICACY

Jean Quancard, Oliver Simic, Carole Pissot Soldermann, Reiner Aichholz, Ina Dix, Karen Beltz, Paul Mcsheehy, Thomas Radimerski, Marc Bigaud, Andreas Weiss, Frederic Bornancin, Achim Schlapbach

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The paracaspase MALT1 has emerged as a key signaling component, mediating activation of several pathways in immune cells, such as NF-kB. In addition, constitutive MALT1 activity is observed in many lymphomas of the activated B cell type sub-types. This has made the search for MALT1 inhibitors an area of intensive research for the treatment of autoimmune diseases and lymphomas. By high-throughput screening, we found MALT1 inhibitors which do not resemble classical cystein protease inhibitors. Using a combination of photoaffinity labeling and NMR studies, we discovered that they bind away from the catalytic site suggesting an allosteric mechanism. Later, X-ray crystallography revealed a unique inhibitory mechanism which prevents the conformational changes that lead to the catalytically active enzyme. From the initial hit, several rounds of scaffold morphing were needed to turn weak, low solubility starting points into potent, orally available molecules. In a subsequent step, *in vivo* potency was optimized by reducing clearance with guidance from metabolism identification studies. PK/PD studies revealed that *in vivo* potency correlates with potency in whole blood. This could be increased by reducing unspecific binding by masking hydrogen bond donors through intramolecular interactions. The resulting compounds show high *in vivo* efficacy in models of autoimmune diseases and lymphomas where MALT1 is overactivated.

Holger MONENSCHEIN

Takeda California, United States

Holger Monenschein received his PhD from the Technical University of Clausthal-Zellerfeld, Germany. Afterwards, he moved to San Diego to conduct post doctoral studies in the group of Prof. K.C. Nicolaou at The Scripps Research Institute, working on the total synthesis of complex natural products. Holger started his industry career at Amgen, Inc. as a medicinal chemist, and quickly became an integral part of the medicinal chemistry department, focusing mainly on diseases of the central nervous system such as Alzheimer's disease and pain. In 2010, Holger moved to Jupiter, Florida where he initiated medicinal chemistry research and discovery at the small biotech startup Envoy Therapeutics. At Envoy, Holger drove the internal drug discovery pipeline from early HTS to the identification of clinical candidates and managed a strong network of supporting CROs to deliver key project data in the fields of in vivo pharmacology, DMPK, and toxicology. In 2013, Holger moved to Takeda California as part of Takeda's acquisition of Envoy. At Takeda he is now director of medicinal chemistry operations in the field of CNS and early target validation.

DISCOVERY OF TAK-041: A POTENT AND SELECTIVE GPR139 AGONIST FOR THE TREATMENT OF NEGATIVE SYMPTOMS ASSOCIATED WITH SCHIZOPHRENIA

Holger Monenschein

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Schizophrenia involves diminished or altered motivation, deficits in social behavior, and difficulties with complex cognitive tasks. Patients often manage their psychoses to some degree with prescription antipsychotics, but there are no effective therapies for the negative and cognitive symptoms, which remain significant unmet medical needs. The habenula is a small nucleus that gates information flow from higher brain centers to the monoaminergic nuclei of the midbrain and brainstem, and is essential for assigning negative value to unrewarding situations. Lesions of the habenula cause deficits in social behavior and cognitive ability, and in schizophrenics, the habenula fails to activate when the patient is challenged with a negative reward. We identified the orphan G-protein coupled receptor GPR139 as a novel excitatory Gq-coupled receptor enriched in the dorsal medial habenula, a small subregion in the habenula that has not been studied extensively. Thus, agonists of GPR139 have the potential to be first-in-class therapies for the treatment of psychiatric diseases with debilitating deficits in social domains such as negative symtoms of schizophrenia.

High-throughput screening of GPR139 yielded promising starting points for medicinal chemistry, which rapidly led to the development of compounds with sufficient potency, selectivity, and brain-penetration to be useful as in vivo tool molecules. In vivo target validation as well as strategies towards the confirmation of in vivo target engagement and PK/PD will be presented in the talk. The first-in-class/first-in-human Takeda GPR139 agonist and molecule TAK-041 will be discussed.

Mike HANN

GlaxoSmithKline, United Kingdom

After completing his PhD in organic chemistry in 1980, Mike has worked in Pharma R&D initially as a medicinal chemist and then as a computational chemist. He joined Glaxo in 1986 and was responsible for helping initially build and then lead the computational chemistry department. More recently he led the biophysics and protein crystallography activities including developing fragments theory and practice in lead identification. His current role is in looking at new technologies to enhance our early drug discovery approaches, particularly to help reduce attrition in drug discovery.

Current interests include new methods to better understanding target tractability and also drug distribution at cellular and subcellular resolution. He is committed to promoting scientific excellence and exchange of knowledge within and across the GSK R&D sites.

Mike is a GSK Senior Fellow and an Adjunct Professor in the chemistry department at Imperial College London.

MOLECULAR ACCESSIBILITY - MEASURING AND UNDERSTANDING THE INTRACELLULAR FREE CONCENTRATION OF DRUGS DURING LEAD OPTIMISATION

Laurie Gordon (1), Andy West (1), Klara Valko (2), Shenaz Bunally (1), Gareth Wayne (1), Chris Luscombe (1,3), Andre Mateus (3), Per Artursson (1,3), Mike Hann (1)

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2) Biomimetic Chromatography Ltd, Business & Technology Centre Unit 5B, Stevenage, SG1 2DX. UK
3) Department of Pharmacy, Uppsala University Drug Optimization and Pharmaceutical Profiling Platform, Uppsala University, SE-751 23 Uppsala, Sweden

We will describe the work we have been doing to understand better the factors effecting the accessibility and availability of free drug at intracellular targets. Understanding the differences between the biochemical and cellular potency of compounds during lead optimisation has historically relied on poorly predictive permeability assays and much hand waving in terms of understanding of lipophilicity and other physchem properties. Furthermore inadequate target exposure has often been cited as a major cause for high attrition in drug discovery. Based on the methodology of and in collaboration with Mateus et al, we have, for the last 3 years, been routinely measuring the actual free and total cell concentration of compounds in HeLa and other cells during the lead optimisation phase [1,2,3]. This presentation will discuss the data on ca. 2k compounds from a wide range of our drug discovery projects at GSK and our interpretation of this data based on measured and predicted physchem parameters, in particular the utility of the chromatographically measured Immobilized Artificial Membrane (IAM) affinity. The availability of this new label-free method for the measurement of the intracellular bioavailability (Fic) of drug molecules provides information on drug accessibility to intracellular targets, a prerequisite for good target engagement. We will also discuss the use of the assay with other cell types including MDCK-MDR1 cells and how it can be used as an alternative assay for recognizing pgp substrates. Finally we introduce a new index for use in lead optimisation which is a normalized version of Fu (the fraction of the total cellular concentration which is free). We refer to this normalised index as NorFu and it is intended to help find compounds with a good free intracellular concentration while not just relying on the total cellular concentration, which can lead to high levels of drug in membranes that is often considered a cause of increased promiscuity.

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Brian RAYMER

Pfizer, United States

Brian Raymer received his B.A. in chemistry from Saint Olaf College (Northfield, MN) where he did undergraduate research in the laboratory of Professor Robert Hanson. He then joined Pfizer as a process chemist, contributing to the Aricept®, Geodon® and Rimadyl® projects. He then moved to Harvard University (Cambridge, MA), completing his Ph.D. studies with Professor David Evans. Subsequently at Novartis, he worked as a medicinal chemist and chemical biologist focusing on low molecular weight, peptide and antibody-drug-conjugate programs in the cardiovascular, metabolic disease and oncology disease areas. Brian returned to Pfizer in 2013 and is currently serving as a Research Project Leader in the Internal Medicine Disease Area.

He has contributed to two clinical candidates in the metabolic disease area, both reaching first-in-human studies and recently chaired the cross-site Pfizer Chemical Biology Network Group.

DISCOVERY OF A KETOHEXOKINASE INHIBITOR FOR THE TREATMENT OF NAFLD/NASH: FRAGMENT-TO-CANDIDATE VIA STRUCTURE-BASED DRUG DESIGN AND PARALLEL CHEMISTRY

Brian Raymer

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Inhibition of ketohexokinase (KHK, fructokinase) may ameliorate non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) by decreasing fructose conversion to fructose-1-phosphate. Initial low-molecular weight hits were identified by fragment screening; subsequent file-mining provided multiple starting points for hit-to-lead chemistry. A combination of parallel synthesis and structure-based drug design yielded an in vivo tool compound that recapitulated the efficacy reported in a KHK-null rodent model on a high-fructose diet. Further optimization provided the clinical candidate, currently in clinical trials. This fragment-to-candidate story will present the fragment-based screen triage, compound optimization via structure-based drug design and parallel chemistry, in vivo target validation, clinical candidate selection and initial clinical data.

Anabella VILLALOBOS

Biogen, United States

Anabella is currently the head of Biotherapeutics and Medicinal Sciences at Biogen, Cambridge, Massachusetts. Prior to joining Biogen, Anabella was at Pfizer for 28 years where she was Vice-President of Medicinal Synthesis Technologies and Neuroscience Medicinal Chemistry. Anabella obtained her B.S. in Chemistry at the University of Panama and her Ph.D. in Medicinal Chemistry at the University of Kansas where she was a Fulbright-Hayes fellow. She was a National Institutes of Health Postdoctoral Fellow at Yale University in synthetic organic chemistry for 2 years.

Among Anabella's accomplishments are her contributions to the design and discovery of CP-118,954 (icopezil), an acetylcholinesterase inhibitor, which was advanced to Phase II clinical trials in Alzheimer's disease. This candidate became part of the agreement that led to the successful co-promotion of Aricept by Pfizer and Eisai. Anabella has championed new scientific directions that have changed design practices in medicinal chemistry such as the Central Nervous System Multi-Parameter Optimization (CNS MPO) design tool. Under her leadership, medicinal chemistry teams have been able to sustain the delivery of quality clinical candidates that have shown increased survival to Proof of Concept (POC) studies in the clinic.

Anabella has also had extensive experience in leading multi-disciplinary teams that have advanced candidates through pre-clinical development and into the clinic, including Phase I and II studies.

Anabella is the author of multiple publications and patents.

NOVEL APPROACHES IN THE DESIGN OF CNS DRUG CANDIDATES AND PET LIGANDS

Xinjun Hou (1), Patrick Verhoest (1), Travis Wager (1), Lei Zhang (1), Anabella Villalobos (2)

1) Pfizer, Cambridge, Massachusetts, U.S.A
2) Biogen, Cambridge, Massachusetts, U.S.A

Over the last few years, the Central Nervous System Multi-Parameter Optimization (CNS MPO) algorithm has been applied prospectively to the design of novel brain-penetrant drug candidates. This design tool, which is based on six fundamental physicochemical properties commonly used by medicinal chemists, provides a flexible, multi-parameter approach rather than focusing on individual properties and hard cut-offs. The use of the CNS MPO has challenged design practices and has resulted in an expansion of the traditional CNS chemical space. It has been demonstrated that CNS candidates which show good brain penetration, ADME properties, and safety profiles can reside in a more polar, less lipophilic, less basic, and larger molecular weight space in comparison to marketed CNS drugs. This new desirability tool has thus challenged the dogma that CNS drugs need to be lipophilic with low polarity and has opened new space for different neuroscience target classes such as kinases and proteases.

Positron Emission Tomography (PET) ligands play a significant role in the CNS drug discovery process. PET ligands are important tools in measuring target occupancy and confirming access to the appropriate tissue in brain. In addition, these ligands have also been used in imaging disease stage and progression. With a goal of bringing a more rational approach to PET ligand development, application of the CNS MPO desirability tool has been extended to the design of novel PET ligands. A modified multi parameter optimization tool, CNS PET MPO, has been put in place together with other property criteria to allow rapid identification of quality PET ligand leads from hundreds of compounds and/or via highly focused structure-activity relationship (SAR) efforts. For each project, only 1-2 leads have been advanced to PET imaging studies to yield a successful PET ligand that performed well in the clinic.

POSTERS

Addressing Preclinical Toxicity – Approaches and Lessons Learned

RET INHIBITORS FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME

John Russell (1), Donghui Qin (1), Amy Guan Huiping (2), Chengde Wu (2), Kaushik Raha (1), Andy King (1), Pete Gorycki (1), Sylvie Laquerre (1), Karl Tyler (3), Eshan Mohammadi (3), Beverly Greenwood-Van Meerveld (3), Allen Oliff (1), Sanjay Kumar (1), Mui Cheung (1), Hilary Eidam (1)

1) GlaxoSmithKline Pharmaceuticals, King of Prussia, PA
2) Wuxi AppTec
3) University of Oklahoma

Irritable Bowel Syndrome, IBS, is characterized by a constellation of clinical symptoms including abdominal pain and discomfort, abnormal bowel habits, and bloating. While the etiology of IBS is incompletely understood, it is thought to arise from either peripheral or central nervous system dysfunction that results in IBS patients having a heightened and disproportionate sensory experience for a given stimulus.

RET is a neuronal growth factor receptor tyrosine kinase critical for the development and survival of enteric neurons. The role of RET in enteric neuron maintenance is exemplified by Hirschprung patients whom carry RET loss of function mutations and lack normal colonic nerve enervation. Therefore, RET signaling, regulated by neurotrophic factor abundance, controls enteric neuron phenotype and morphology. Inhibition of RET in the enteric nervous system of the colon represents a novel mechanism of action for the normalization of visceral hypersensitivity in IBS patients. A screening effort lead to the discovery of a series of potent, selective, and developable RET inhibitors that are gut restricted. The evolution of the program from screening hit to developable compounds will be discussed, including the hurdles that have been overcome in advancing a compound with a novel target for IBS.

POSTERS

Advances in Lead Generation

ANALOGUES OF DESFERRIOXAMINE B DESIGNED TO ATTENUATE IRON-MEDIATED NEURODEGENERATION: SYNTHESIS, CHARACTERISATION AND ACTIVITY IN THE MPTP-MOUSE MODEL OF PARKINSON'S DISEASE

Michael Gotsbacher (1), Thomas Telfer (1), David Finkelstein (2), Rachel Codd (1)

1) School of Medical Sciences (Pharmacology) and Bosch Institute, The University of Sydney, Sydney, Australia
2) Florey Dept. of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia

The death of dopaminergic neurons in the substantia nigra (SN) is characteristic of Parkinson disease (PD) [1]. Iron content within the SN region in PD is elevated and argued to catalyse the disease progression through iron-mediated oxidative damage caused by reactive oxygen species (ROS) [2]. Hence, removal of excess iron is a potential therapeutic strategy.

Desferrioxamine B (DFOB), a natural iron chelator with high Fe(III) affinity (Log*K*a 30) and low toxicity, has a long clinical history for treating iron overload disease in patients with β-thalassemia. However, its high water solubility attenuates its ability to enter the brain. In previous studies, lipophilic DFOB analogues were shown to out-perform DFOB in PD *in vitro* models [3].

We have conjugated DFOB to clinically relevant antioxidants and one adamantyl derivative to ***(a)*** produce lipophilic compounds designed to increase the bioavailability of DFOB to brain cells and ***(b)*** act as antioxidant in dual mode by chelating Fe(III) and scavenging ROS.

We have determined that the novel compounds display LogP values (mean LogP_{Oct} = 1.9) that are similar to those of successful CNS-drugs (cLog*P* = 2-4), are stable in plasma (except one), show plasma protein binding of 75-97%, and are effective antioxidants in the iron-mediated ascorbic acid oxidation and antiradical ABTS assays. Selected compounds progressed to animal studies using the MPTP mouse model of PD, resulting in significant reduction of striatal neuron loss in comparison to DFOB and vehicle (Fig.1) [4]. These novel compounds have potential as therapeutics for the treatment of PD and other conditions of iron dyshomeostasis.

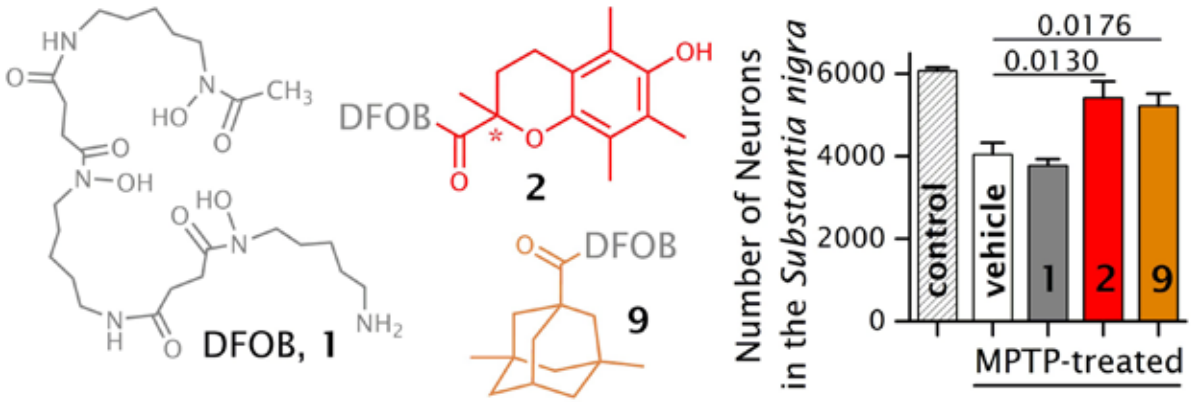

Fig. 1: Seven dual-function desferrioxamine B (DFOB, **1**) conjugates (**2**-**8**) were designed to abrogate oxidative stress by chelating redox-active Fe(III) and deactivating reactive oxygen species (ROS) at ancillary antioxidant groups. One dual-function (**2**) and one first-generation (**9**) compound showed significant rescue of neurons ($p < 0.05$; up to 89% of that in control animals) in the MPTP mouse model of Parkinson's disease.

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THE DEVELOPMENT OF NOVEL COMPOUNDS AS POTENT AND SELECTIVE INHIBITORS OF KINASES INVOLVED IN ALTERNATIVE SPLICING

Tom Hawtrey (1), Veronica Tecchio (1), Belinda Huff (1), Stefan Knapp (2), Jonathan Morris (1)

1) School of Chemistry, University of New South Wales
2) Institute for Pharmaceutical Chemistry and Buchmann Institute for Life Sciences, Johann Wolfgang Goethe-University, Frankfurt, Germany

Alternative splicing of mRNA is a key process responsible for generating protein diversity in higher organisms. This is achieved by the generation of multiple protein isoforms from single genes.[1] The balance of the protein isoforms that result from alternative splicing is crucial for maintaining good health and proper cell function, with many diseases involving the dysregulation of particular proteins.[2] For this reason, controlling the alternative splicing events that govern the production of these proteins is essential in the study of these diseases and in the search for viable therapeutic options to treat them.

Kinases are one of the groups of enzymes responsible for regulating alternative splicing, with the CLK, DYRK and SRPK families of kinases among those involved. Small molecules have been used to modulate the function of these kinases, however these have often displayed poor selectivity for the closely related kinases. Achieving this selective inhibition is crucial for properly understanding the role of these kinases in alternative splicing and in disease.

My work has investigated several novel scaffolds, including the pyrrolo[1,2-c]pyrimidines, for use as inhibitors of these kinases in a manner that is both potent and selective. Our approach has utilised molecular modeling to design compounds which possess selectivity for these kinases, followed by the synthesis of a number of analogues and finally biological evaluation performed by our collaborators. A library of compounds has been prepared and their synthesis and biological activity will be described.

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POSTERS

Advances in Synthetic Methods

NOVEL BICYCLO[1.1.1]PENTANE (BCP) BUILDING BLOCKS BY THIOL ADDITION TO [1.1.1]PROPELLANE

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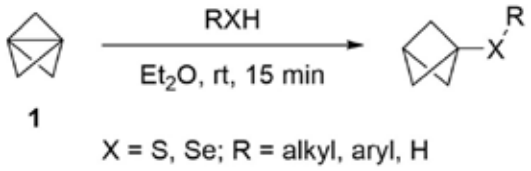
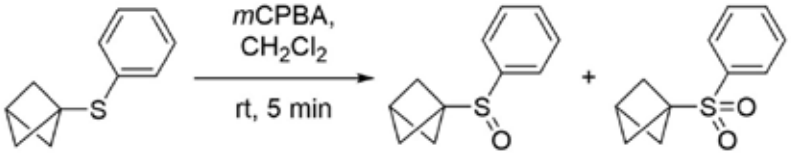
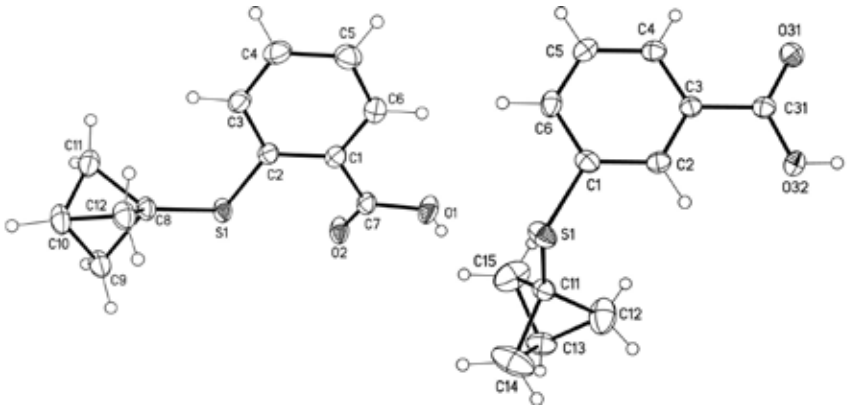
We report the addition of different thiols to the strained carbon-carbon bond of [1.1.1]propellane (**1**). We investigated the reaction pathway, performed the addition with substituted thiols, hydrogen sulfide and protected cysteine and verified further modifications of the products. The clean reaction proceeds probably through a radical chain process as we confirmed with different deuterium labelling experiments. It shows great functional group tolerance as halogen-, hydroxy-, methoxy-, carboxy-, amino- and nitro-substituted thiols could be added to **1** with few by-products in 16–90% yield. The "click"-type reaction proceeds even faster with selenols as we show in a proof-of-concept.



Oxidation of the products offers a tuning of the polarity and subsequent reactions of the products.



Additionally we could determine the structure of two bicyclo[1.1.1]pentylsulfides with single crystal X-ray diffraction. To the best of our knowledge this is the first report of a crystal structure of terminal BCP-sulfides.



The thiol addition to **1** offers a facile tool for surface modifications, conjugations and tuning of hydrophilicity in bio- and medicinal chemistry compounds.

THE FIRST ENANTIOSELECTIVE INTRAMOLECULAR CARBONYLATIVE HECK-MATSUDA REACTION

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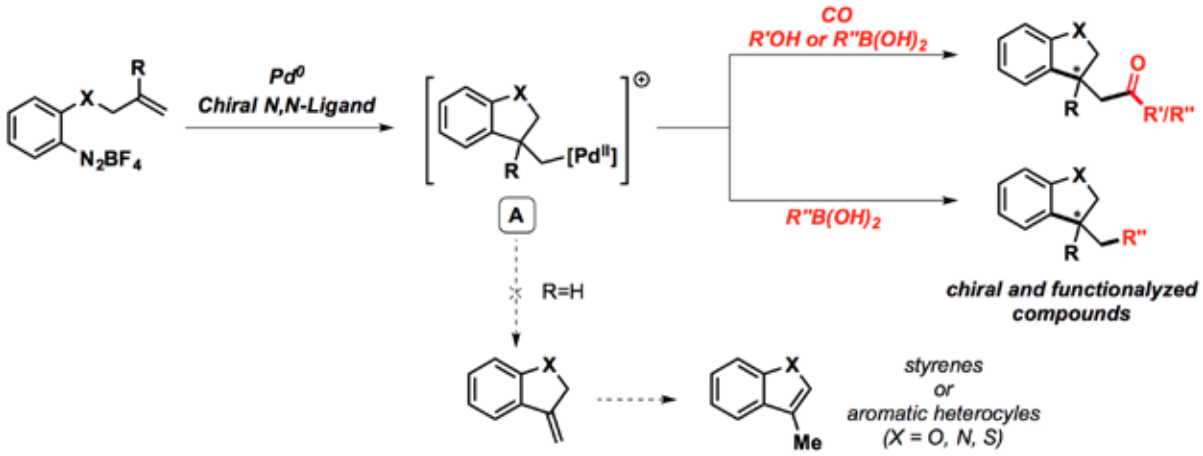
Efficient methods to construct carbon-carbon bonds have been the main aim of organic chemists. The Heck reaction, a palladium-catalyzed functionalization of olefins with an electrophile, is a powerful tool and one of the most used transformations.[1] The use of arenediazonium salts as electrophiles, known as Heck-Matsuda reaction, is increasingly contributing to the synthesis of valuable compounds in a practical and efficient manner. In the last few years, the Correia group has been studying and improving the aspects in respect with the asymmetric intermolecular variant of this reaction and the use of many classes of olefins have been reported.[2]

The asymmetric intramolecular Heck-Matsuda reaction has never been reported before, mainly due to instability of the arenediazonium salt and the rapid formation of styrenes and/or aromatization of the intermediate. Herein we report the first examples in carbonylative intramolecular Heck-Matsuda reactions (Scheme 1).



Scheme 1. Enantioselective Intramolecular Cascade Heck-Matsuda Reaction

In summary, we have been investigating the palladium trapping intermediate A with CO/alcohols and also with boronic acids from the intramolecular enantioselective Heck cyclization.

We acknowledge the São Paulo Research Foundation (grant 2013/10183-5) for studentship and University of Campinas for support.

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HIGH-THROUGHPUT LIBRARY SYNTHESIS IN MEDICINAL CHEMISTRY

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The driver for medicinal chemistry is the demand for innovative medicines. Typically the growing need for novel active ingredients is accompanied by the search for targeted molecular diversity and novel experimental routes resulting in an increase of the synthetic work with the same amount of human resources. The only way to cope with this catch22 are flexible, modular, uncompromising automated solutions for library synthesis.

Following a brief introduction to concepts and Chemspeed's innovation enabling technology, this presentation will focus on selected case studies from our customer portfolio such as:

- Synthesis of a triazole library using automated click chemistry.
- Development of a first generation MKP-1 probe.
- Discovery of an α-amino C–H arylation reaction using the strategy of accelerated serendipity.
- Synthesis of an oxazolidinones library using solid phase organic synthesis.
- Development of nanoparticle drug discovery vehicles.

ACID-INDUCED TRANSFORMATIONS OF INDOL YNONES LEADING TO THE FORMATION OF SPIROINDOLENINES AND QUINOLINES

Pavel Fedoseev, Guglielmo Coppola, Gerardo Ojeda, Erik Van der Eycken

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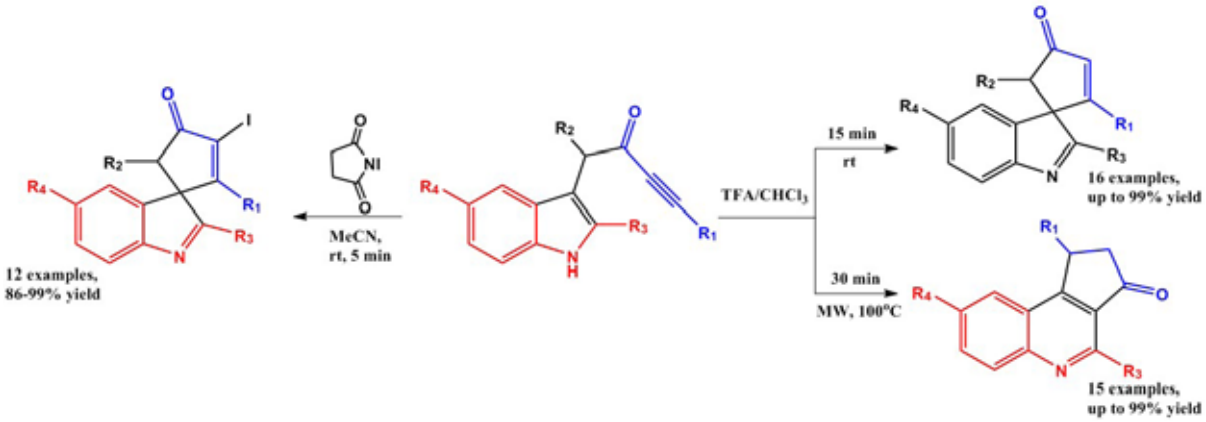
We present a high-yielding approach of Brønsted and Lewis acid annulation of indol ynones leading to corresponding spiroindolinines without the well known and expected formation of a 1,2-rearranged products.



The application of TFA and NIS leads to the formation of the products in up to quantitative yields. Increasing the temperature in case of TFA catalysis lead to the formation of quinolines following a rearrangement. Optimization tables, reaction scopes and plausible mechanisms are presented.

EXPLORING PUMMERER CHEMISTRY TO SYNTHESIZE NEW HETEROCYCLIC SYSTEMS

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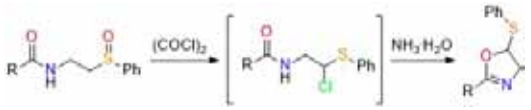
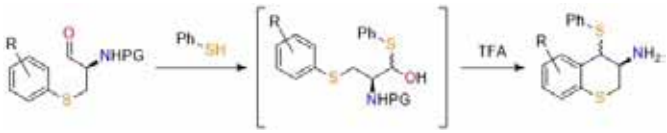
Heterocyclic compounds are one of the most important scaffolds in organic chemistry. They are involved in virtually all biological processes and distributed in nature with a great structural variety. The diversity in the chemical behavior of heterocycles had allowed to use them in many research areas as agrochemicals, polymer precursors, dyes, drugs, and many others. Despite the synthetic interest in heterocycles, existing methodologies for their synthesis lack mild conditions, generality, and atom economy.[1-3] On the other hand, Pummerer reaction is an interesting alternative for constructing heterocyclic compounds, since it allows the formation of carbon-carbon and carbon-heteroatom bonds through the addition of a nucleophile to a thionium ion.[4]

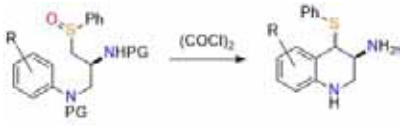
We have developed new strategies for the synthesis of some heterocyclic systems using Pummerer chemistry under mild reaction conditions. We were able to prepare 5-thiosubstituted oxazolines by a Pummerer reaction of a sulfoxide followed by an intramolecular nucleophilic substitution (scheme 1).[5] Also, we synthetized chiral 3-aminothiocrhomanes employing a connective Pummerer reaction with the aromatic ring of an aldehyde derived from phenylcysteine as the nucleophile (scheme 2). Furthermore, we could access chiral 3-aminotetrahydroquinolines by an intramolecular Pummerer reaction of a sulfoxide (scheme 3). This methodology is operationally simple and proved to be general as it tolerates various substituents without losing efficiency.



Scheme 1. Oxazoline synthesis *via* intramolecular Pummerer reaction.



Scheme 2. 3-Aminothiochromane synthesis *via* connective Pummerer reaction.



Scheme 3. 3-Aminotetrahydroquinoline synthesis *via* intramolecular Pummerer reaction.

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ROOT CAUSE OF BY-PRODUCT FORMATION IN A HYDROGENATION REACTION

Sonja Kamptmann

Novartis Pharma AG, Basel

Researchers at Novartis turned to in situ techniques that allow scientists to perform data rich experiments. Although integrating PAT tools can provide comprehensive and continuous analysis of the reaction in real time, critical information concerning low level impurity profiles is limited with these techniques. Offline techniques such as HPLC, UPLC, and GC are considered to be the standard for impurity analysis, but sampling hydrogenations under pressure is challenging due to cumbersome manual sampling protocols. Understanding the mechanism of a by-product formation requires identifying in which step of the reaction the by-product is formed, and then determining which parameters cause the by-product formation. Capturing information for better mechanistic understanding which helped in the development of a chemical process is outlined in the shown poster.

STEREOSELECTIVE SYNTHESIS OF CIS-2,3-DISUBSTITUTED INDOLINES VIA METAL-FREE REACTIONS

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Indolines are structurally essential elements in biologically active natural compounds and are extremely important in medicinal chemistry being widely used as pharmacophores in drug discovery.[1] Indole skeleton, which is ubiquitous in nature and used in different purposes in chemistry, biology and material sciences, is also one of the privileged structure.[2] Consequently, the development of synthetic methods for 2,3-disubstituted indolines and remains a great challenge in synthetic organic chemistry.

We recently demonstrated the method for the construction of *cis*-2,3-disubstituted indolines which has been developed through an aza-alkylation/Michael cascade reaction of 2-(tosylamino)phenyl α,β-unsaturated ketones with α-bromoacetophenone.[3] This simple domino process afforded diverse highly functionalized indolines in high yields with good diastereoselectivities. We also developed the method for the asymmetric synthesis of enatioenriched 2,3-disubstituted indolines via an organocatalytic intramolecular Michael addition. When a primary amine derived from cinchona alkaloid was used as the catalyst, the intramolecular cyclization reaction of (*E*)-3-(2-(2-oxopropylamino)aryl)-1-alkylprop-2-en-1-ones afforded *trans*-2,3-disubstituted indolines in high yields and with good-to-excellent diastereo- and enantioselectivities (up to 20:1 dr and 99% ee).

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NEW CYCLOBUTYL AMINES AND AMINO ACIDS: SYNTHESIS AND PHYSICAL-CHEMICAL PROPERTIES

Ivan Kondratov (1,2), Nataliya Tolmachova (1), Illya Feskov (1,2), Anton Chernykh (1), Günter Haufe (3)

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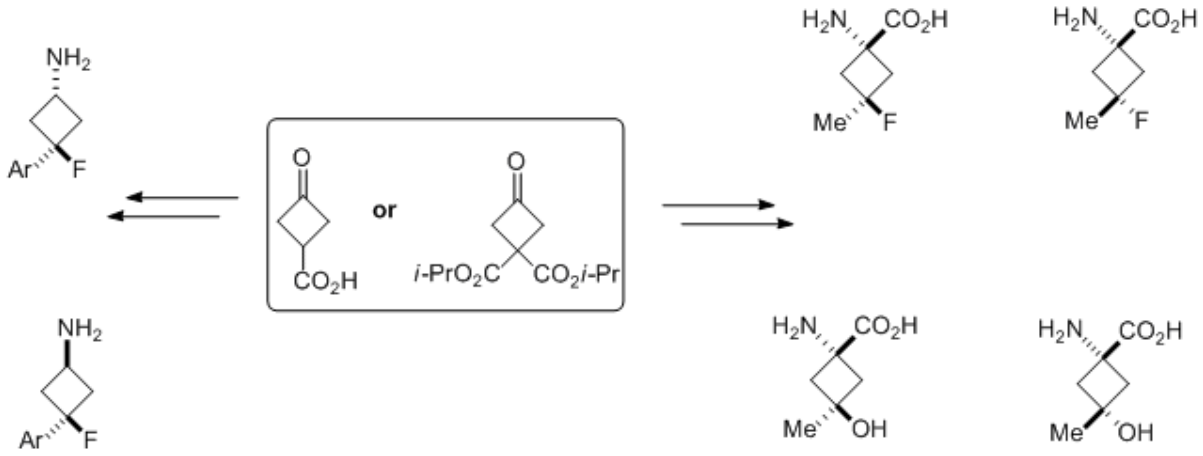
3) Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, 48149 Münster, Germany

Among the cyclic systems, 1,3-disubstituted cyclobutanes possess attractive features for drug discovery since they are achiral due to the presence of a symmetry plane that makes them convenient targets from the synthetic point of view. Often the corresponding diastereomers can be synthesized selectively or can be easily separated. Moreover, they are attractive moieties for drug discovery (e.g. as restricted mimetics of alkyl chains) and numerous compounds bearing this motif found various applications as biologically active substances including several drug candidates in the clinic.

In this report we present a straightforward synthetic approach to hitherto unknown 3-(aryl/methyl)-3-fluorocyclobutyl amines and 3-methyl-3-fluoro/hydroxyl cyclobutyl amino acids from commercially available nonfluorinated cyclobutanes. The developed sequence led to diastereomeric pairs of the target compounds, which were separated and used to determine their physical-chemical properties such as lipophilicity and pK_a values.

Detailed synthetic approaches, as well as physical-chemical data, will be discussed in the presentation.



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MARINOQUINOLINES AS ANTIMALARIAL AGENTS: DESIGN OF NEW HIGHLY ACTIVE AND SELECTIVE DERIVATIVES

Patrícia Santos Barbosa (1), Eric Francisco Simão dos Santos (1), Michele Panciera (1), Anna Caroline Campos Aguiar (2), Mariana Lopes Garcia (2), Guilherme Eduardo de Souza (2), Rafael Vitório Carvalho Guido (2), Carlos Roque Duarte Correia (1)

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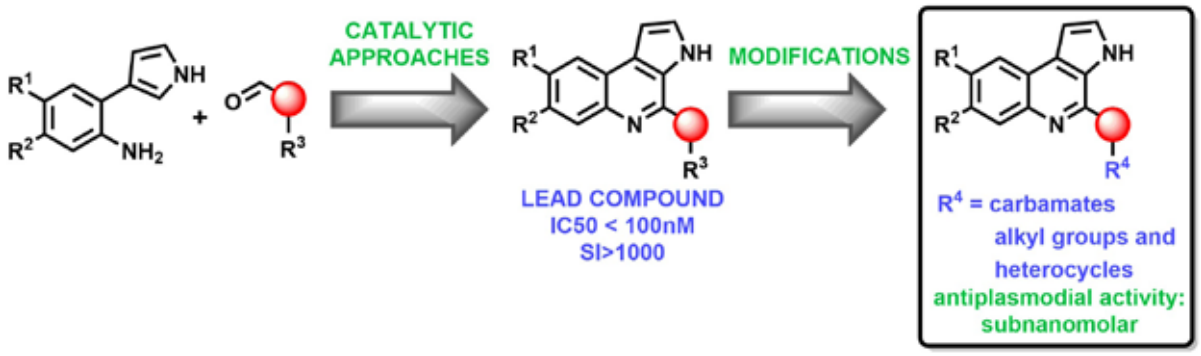
The natural marinoquinolines isolated from *Rapidithrix thailandica* and *Ohtaekwangia kribbensis* are known to have antimalarial activity. [1] In a previous study conducted by our group, we discovered a marinoquinoline derivative as lead compound for the development of new antimalarials. The compound is a potent inhibitor of parasite growth (IC_{50} < 100 nM against *Plasmodium falciparum* 3d7 strain) with high selectivity index (SI > 1000). A new series of marinoquinoline derivatives was designed based on QSAR models, providing molecular insights for the synthesis of new derivatives. To obtain the analogues we used Pictet-Spengler reaction [2] as well as modifications using carbamates, alkyl groups, and heterocycles. The new derivatives are inhibitors of *P. falciparum* growth with activity in the subnanomolar range.



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STEREOSELECTIVE SYNTHESIS OF GEM-DIFLUOROALKENES VIA LANTHANIDE-MEDIATED C-F ACTIVATION

Tarun Kumar (1), Fabien Massicot (1), Dominique Harakat (1), Sylviane Chevreux (1), Agathe Martinez (1), Amira Ben Hassine (1), Klaudia Bordolinska (1), Preethanuj Preethalayam (2), Radhakrishnan Kokkuvayil Vasu (2), Jean-Bernard Behr (1), Jean-Luc Vasse (1), Florian Jaroschik (1)

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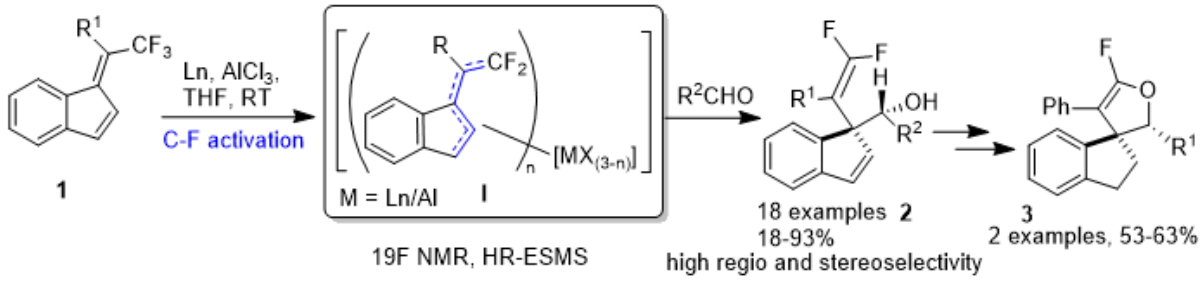
Fluorinated compounds have received significant attention due to their applications in metarial science, agrochemicals, pharmaceuticals and catalysis.[1] Incorporation of fluorine can alter metabolic stability, lipophilicity and binding affinity in many drug molecules.[2] *gem*-Difluoroalkenes among other fluorinated compounds have been intensive subject of study because of their potential biological activities and their ability to react with wide range of nucleophiles.[3] Difluoroalkenes can serve as excellent electrophile and can easily undergo to addition-elimination reaction with nucleophiles to give mono-fluorinated compounds. In present work, the synthesis of difluoroalkene containing molecules **2** from selective single C-F activation in benzofulvenes **1** having an exocyclic CF_3-substituent has been discussed. This C-F activation reaction is promoted by using a combination of lanthanide metal and $AlCl_3$. This reaction proceeded via metal-dienyl species **I** and the intermediacy of such species was confirmed by ^{19}F NMR and HRMS studies. Subsequently, the metal dienyl intermediate was treated with a range of aldehydes to give differently substituted difluoroalkenes **2**. These difluoroalkenes were further transformed to spiroindanes **3**. The reactivity of metal dienyl species with other electrophiles and transmetallation will also be discussed.



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ALKENE OXYAMINATION USING MALONOYL PEROXIDES: PREPARATION OF PYRROLIDINES AND ISOXAZOLIDINES

Carla Alamillo-Ferrer (1), Simon C. C. Lucas (1,2), Stuart C. Davidson (1), Stephen J. Atkinson (2), Matthew Campbell (2), Alan R. Kennedy (1), Nicholas C. O. Tomkinson (1)

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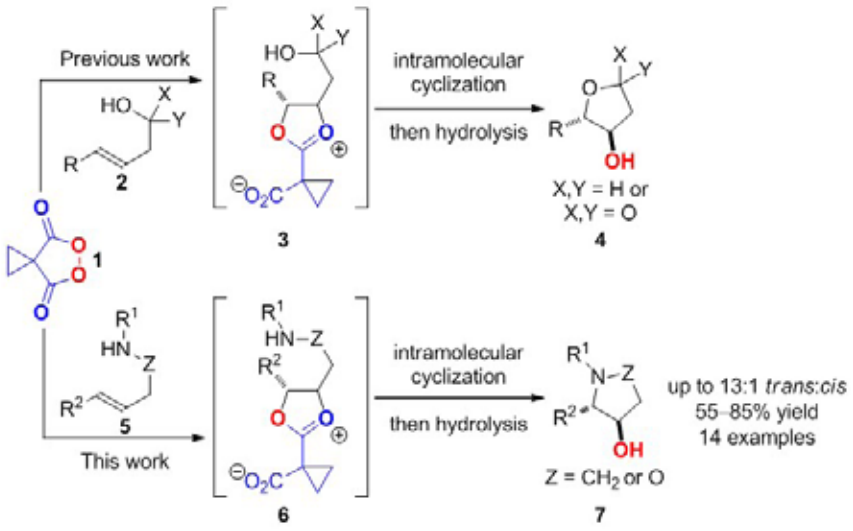
2) GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom

Malonoyl peroxides 1 are well established as effective reagents for the metal-free syn- and anti-dihydroxylation of alkenes.(1) An oxidative heterocyclization procedure has also been developed and used to prepare biologically relevant saturated heterocycles 4 from readily available precursors 2.(2) Building on this work we looked to see if we could optimise the reactivity of a nitrogen nucleophile 5 in order to induce an oxidative oxyamination heterocyclization.

Within this poster we will describe the intramolecular, stereoselective, metal-free oxyamination reaction for the preparation of pyrrolidines and isoxazolidines 7 using malonoyl peroxide 1. Reactions proceed in 55-85% yield with a trans-selectivity of up to 13:1. Evidence to explain the mechanistic course and stereochemical outcome of the transformation will also be presented.



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CONCISE BIOMIMETIC TOTAL SYNTHESES OF MEROTERPENOIDS FACILITATING THE DISCOVERY OF NEW CLASSES OF PHARMACEUTICALS

Tsz-Kan Ma, Anthony G. M. Barrett

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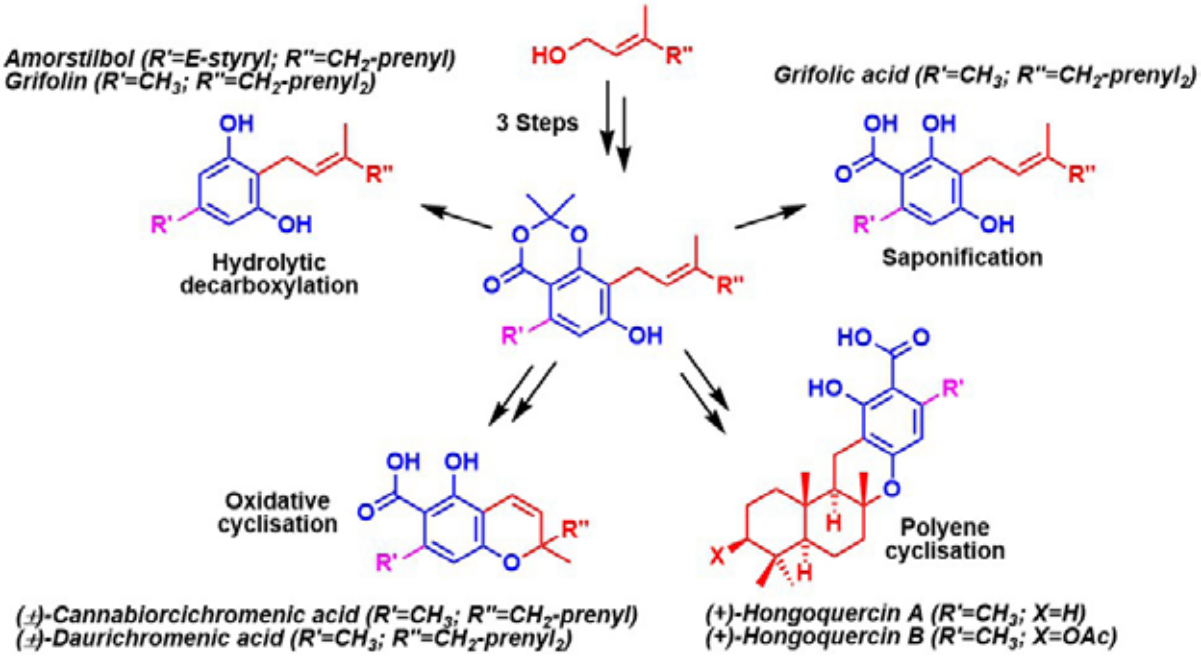
Meroterpenoids are hybrid natural products with mixed biosynthetic origin involving the polyketide and terpenoid pathways.[1] Due to the fact that some meroterpenoids were found to be bioactive and are potential hits to infectious diseases and cancer, there is a need to develop concise yet flexible synthetic route to these molecules for further structure-activity relationship (SAR) studies.

Inspired by the pioneering work of Harris *et al*[2] and Hyatt *et al*[3] on β-resorcylates and dioxinone thermolysis, we developed a concise biomimetic route to β-resorcylates. More recently, we established an efficient protocol for the preparation of dioxinone beta-keto esters based on the reaction of allylic alcohols with dioxinone-acyl-ketenes.[4,5] Application of our recent findings allows rapid access to terpene resorcylates in 3 steps from commercially available terpene alcohols without the use of protecting groups. The resulting terpene resorcylates could then be transformed into a selection of meroterpenoid natural products concisely and this synthetic route is suitable for analogue syntheses.



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INVESTIGATION OF OXETANES AND STRAINED ALIPHATIC RINGS AS ISOSTERES IN MEDICINAL CHEMISTRY

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2) Department of Chemistry, Imperial College London
3) Department of Chemistry, Oxford University

Moving away from the 'aryl flatland', in addition to developing new structural motifs to improve drug-like properties remains a key topic of interest in drug discovery, and presents an intriguing challenge to synthetic organic chemistry. Moving towards increased sp3 character in targeted pharmacologically relevant molecules often leads to improved property space, while simultaneously opening new vectors accessible to drug design. The work described herein delineates our efforts in collaboration with the Bull group at the Imperial College London to develop new synthetic methods to the facile access novel 3,3-disubstituted oxetanes. These methods have been applied towards the synthesis of complex molecules with drug-like properties whose physicochemical properties have been studied to determine their feasibility as ketone, amide, and thioester isosteres. In addition, we will describe our efforts with the Anderson group at Oxford University towards the synthesis of highly decorated, functionalized [1.1.1]-bicyclopentanes with potential application as phenyl and alkynyl isosters.

BUILDING-UP MOLECULAR COMPLEXITY WITH CARBENOIDS: NEW CONCEPTS IN HOMOLOGATION CHEMISTRY

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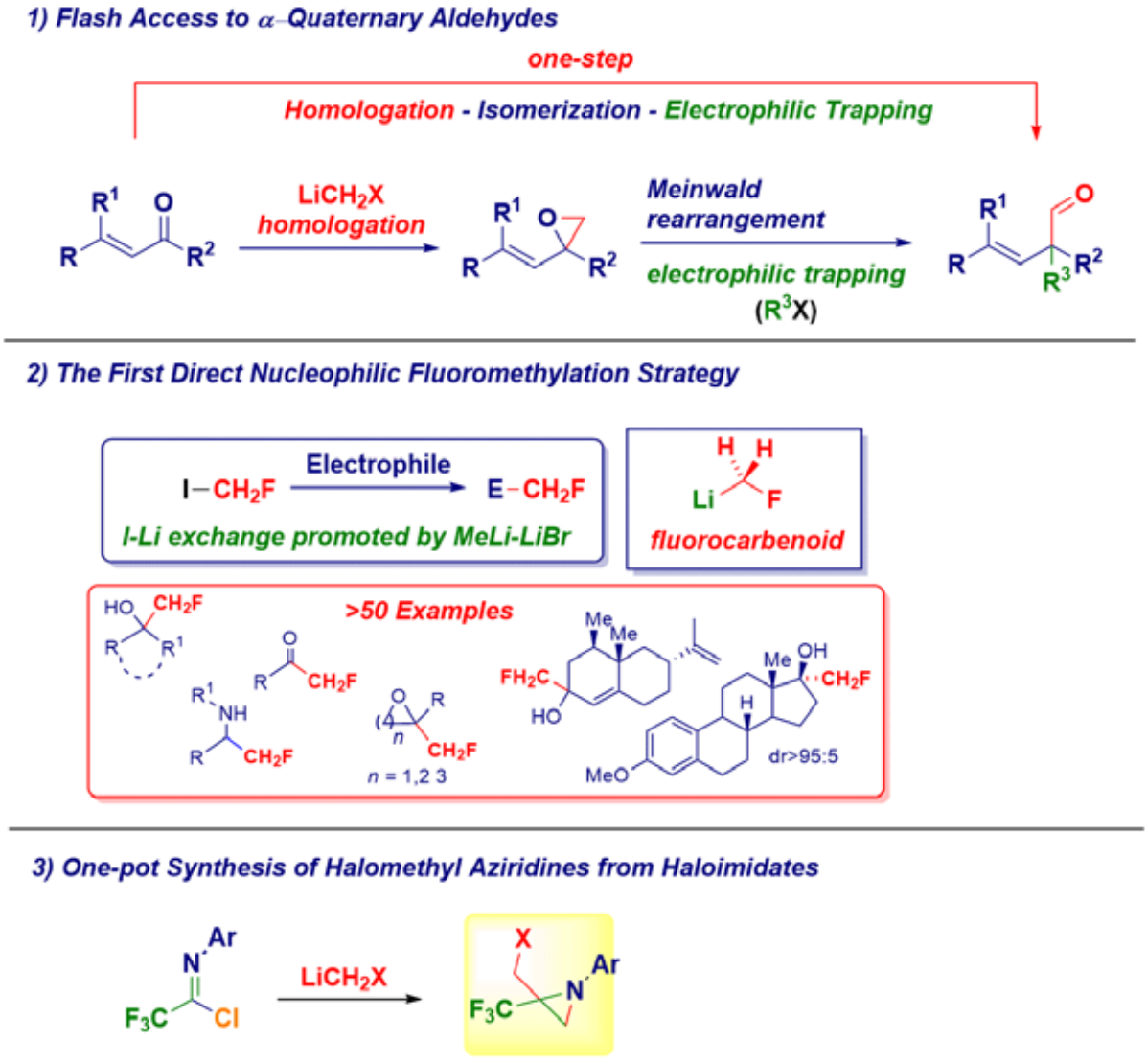
Homologation chemistry with carbenoid reagents represents nowadays an established tool for synthetic chemists with focus on medicinal applications. As documented in recent work by our group, these reagents enable the construction of a new functionalized C-CH_2X bond through a single synthetic operation thus, making rapid the installation of a reactive fragment.[1] New reactivity concepts for the straightforward construction of complex building blocks through a single synthetic operation will be presented. 1) A flash access to α-quaternary aldehydes;[2] 2) The employment of fluoromethyllithium as nucleophile[3] and, 3)The one-pot synthesis of halomethyl aziridines from haloimidates.[4]



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RHODIUM(III)-CATALYZED INTRAMOLECULAR ANNULATION THROUGH C-H ACTIVATION: CONCISE SYNTHESIS OF ROSETTACIN AND OXYPALMATIME

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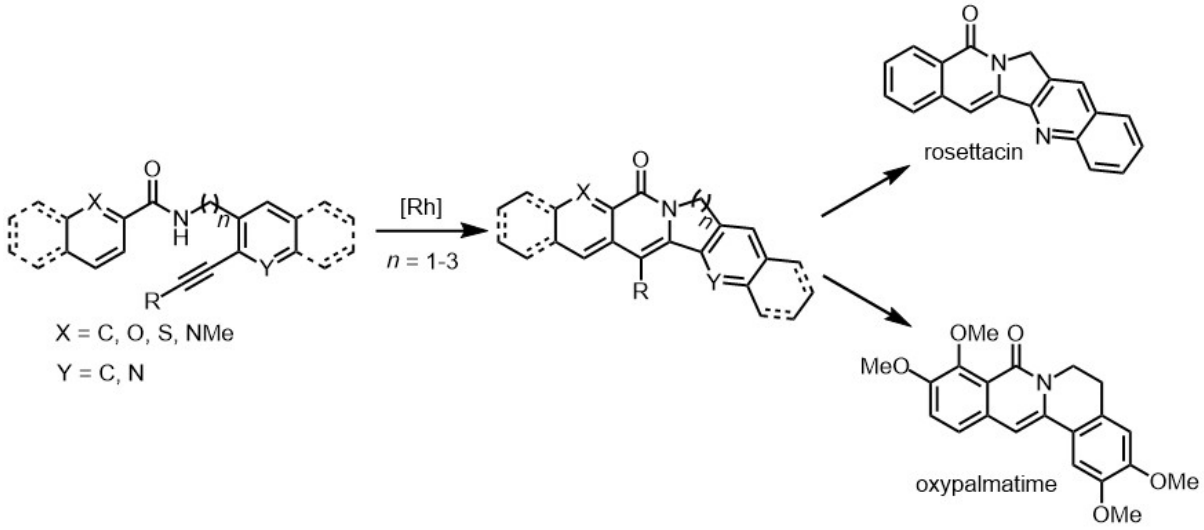
A flexible and efficient rhodium(III)-catalyzed intramolecular annulation of bearing alkyne-tethered benzamides for the synthesis of indolizinones and quinolizinones is reported. This reaction shows a broad substrate scope and excellent functional-group tolerance, including different kinds of heterocyclic substrates, such as furan, thiophene, pyrrole, benzofuran, benzothiophene, indole and isonicotinamide substrates. This method also provides a practical and efficient approach for the synthesis of rosettacin and oxypalmatime.



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HYPERVALENT IODINE(III)-MEDIATE CASCADE CYCLIZATION OF PROPARGYLGUANIDINES AND TOTAL SYNTHESES OF KEALIININE B AND C

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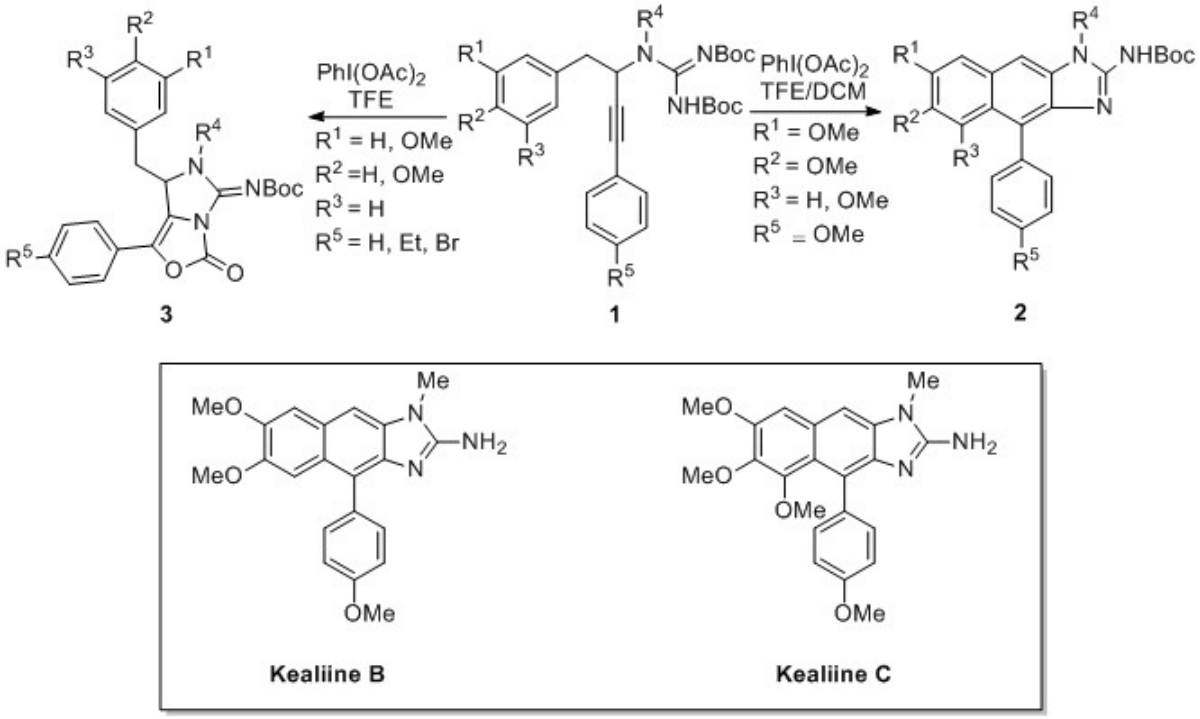
An oxidative cascade cyclization of propargylguanidines promoted by phenyliodonium diacetate (PIDA) was developed. The protocol provides an efficient route for the synthesis of the alkaloids kealiinines B and C as well as homologues. The difference in the electronic nature of the acetylene substituent resulted in two ways of the cyclization.



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SPECTROSCOPIC STUDIES OF THE CHAN-LAM AMINATION: A MECHANISM INSPIRED SOLUTION TO THE BORONIC ESTER REACTIVITY

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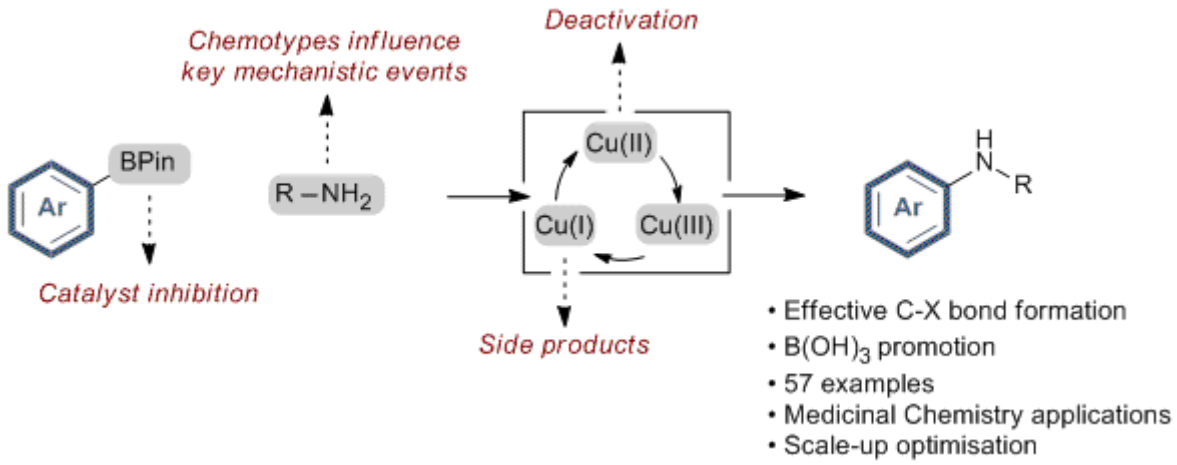
An investigation of the Chan-Lam amination reaction will be discussed,[1,2] providing a full mechanistic description, including the source of the boronic acid pinacol ester (BPin) problem, determining the origin of amine chemotype reactivity and side reaction issues, identifying key reactive intermediates, and demonstrating the pivotal role of boron-based by-products.[3] A simple solution manipulating Cu(I)→Cu(II) oxidation and exploiting three synergistic roles of boric acid will be described. This has allowed the development of a general catalytic Chan–Lam amination and enhanced the practice of this useful transformation in both medicinal and process chemistry at GSK.[3]



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SYNTHESIS OF TROPOLONE NATURAL PRODUCTS USING THIOPHENE-1,1-DIOXIDES

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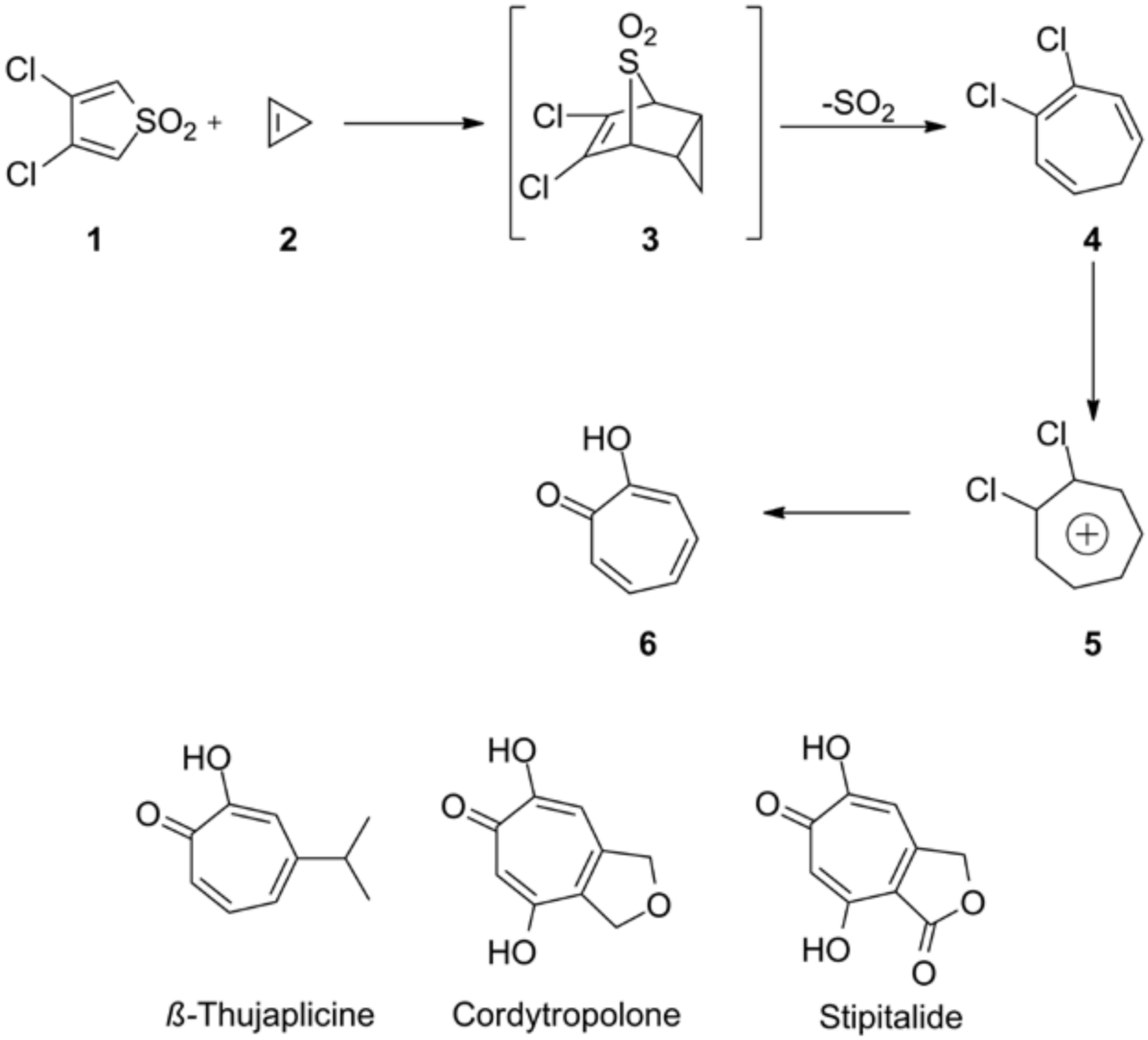
Thiophene-1,1-dioxides are a highly versatile group of compounds that, to date, have been underutilised in organic synthesis[1-3]. These molecules can participate in a range of reactions, including the Diels-Alder reaction. When cyclopropenes react with thiophene-1,1-dioxides the Diels-Alder adduct spontaneously eliminates sulfur dioxide to form a cycloheptatriene[4]. By performing this reaction with a substituted thiophene dioxide, such as 3,4-dichlorothiophene-1,1-dioxide **1**, substituted cycloheptatrienes can easily be produced. The cycloheptatriene **4** could then be converted to tropolone **6** via the tropyllium cation **5**. This offers a versatile way to form tropones and tropolones. Substituted cyclopropenes could easily be used to produce natural products such as *ß* -thujaplicine as well as bicyclic natural products such as cordytropolone and stipitalide.



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STRATEGIES FOR THE SYNTHESIS OF CHROMANES AND 3-AMINOCHROMANES

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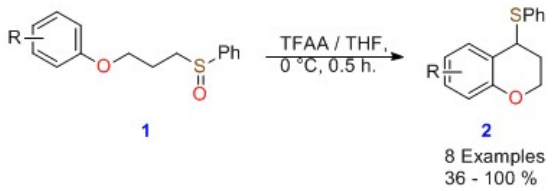
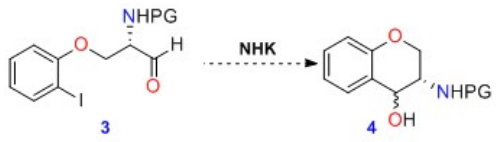
Benzodihydropyrans, also called chromanes, are heterocyclic compounds with a valuable structural core due to their biological activity. Those nucleus can be found in several drugs and are recognized as a pharmacophore with multiple therapeutic applications: antiplatelet,[1] antioxidant,[2] antitumoral, antiviral, and analgesic properties, [3] among others. Because of its biological properties, the synthesis of these scaffold has been studied and successfully achieved employing different methodologies that are mainly based in multicomponent condensation reactions of phenols and aromatic aldehydes.[1] Other synthetic pathways involve intramolecular oxa-Michael/Friedel-Craft tandem reaction from phenols and β-γ unsaturated α-ketoesters,[4] the used of phenylselenyl chloride for the treatment of 3,3-dimethylallyl and propenylbenzene ethers of differently substituted phenols,[5] and radical reactions over (3-iodopropoxy)benzenes.[6] Nonetheless, some of the reported methodologies present disadvantages that limit their application in the synthesis of these core like hazardous conditions, low yields, poor regioslectivity and employment of expensive catalysts.

In order to obtain these structural core we have proposed two different synthetic pathways. The first one, involves a classical intramolecular Pummerer reaction to obtain a C-C bond over (3-(sulfinyl)propoxy)benzenes. These method provide the expected chromanes with good to excellent yields under mild conditions (Scheme 1). The second synthetic pathway is the application of the Nozaki-Hiyama-Kishi reaction over 3-(2-iodophenoxy)propanaldehydes in order to achieve the pyranic ring (Scheme 2).



Scheme 1. Chromane synthesis via intramolecular Pummerer reaction.



Scheme 2. Synthesis of 3-aminochromane via Nozaki-Hiyama-Kishi reaction.

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POSTERS

Alternative Modalities

σ-HOLES —REALLY THAT STRONG? THE IMPACT OF WATER ON AFFINITY

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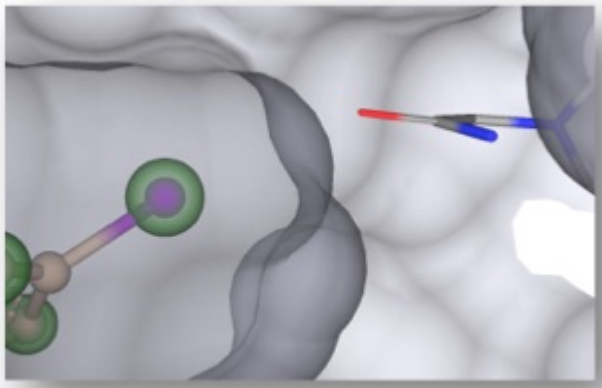
Over the past years, σ-holes[1] (the localized electron deficiency of polarizable halogen atoms leading to favorable electronic interactions with Lewis bases) have experienced vivid discussions and broad published awareness. Some drug researchers have recently started to incorporate the halogen binding concept into their rationalizing of lead optimization.[2]

In this talk we will shine light on the fine difference between *correlation* versus *causality*, and - using a multitude of examples - we will analyze the impact of these clearly physical, electronic effects on binding affinity.



We will balance the effect of water versus σ-holes onto substrate and drug binding using affinity measurements that shall be compared to both an empirical, logP-based model [3] and advanced quantum chemical computations. A broad geometric analysis of complexes in the PDB using a recently developed academic software [4] supports the assumption that the overall energetic contributions are almost negligible in an aqueous environment, and that the expected geometries are only very rarely found in protein-ligand crystal structures. Conclusions and consequences for rational design shall be discussed.
Whereas most electron structure calculations quantify σ-hole interactions in an *in vacuo* context, it is important to note that water plays an additional, very important role in the definition and thus calculation of binding affinities in a drug design context.

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'NEXT GENERATION' ANTIBODY CONJUGATION

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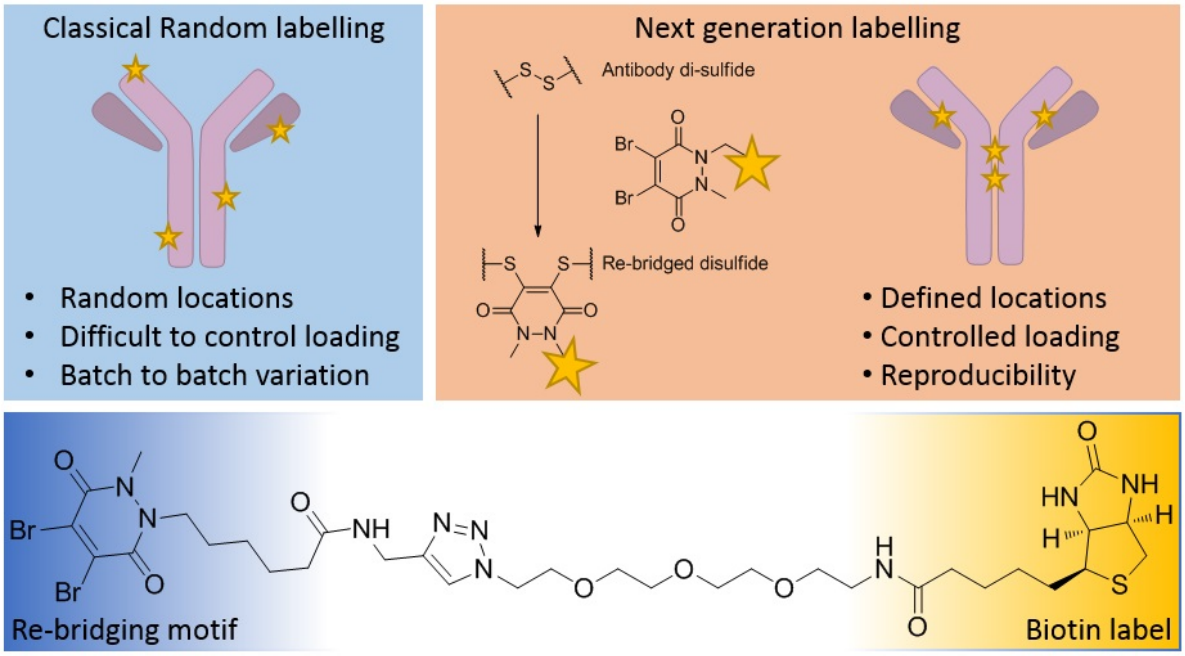
It has been over a century since Paul Ehrlich proposed the concept of the 'magic bullet' for tailored and targeted drug delivery in fighting against human diseases. Today, antibody drug conjugates (ADC) offer specific targeting of a cytotoxic drug to a cell population [1] although this promising class of therapeutic has been mainly limited to cancer therapy. Recent developments in antibody conjugation have enabled the synthesis of much more homogeneous, stable ADC and these advances together with deeper understanding of the hurdles associated with ADC development may open the field to non-oncology targets. [2] The specific and controlled conjugation of a small molecule payload to an antibody may also have benefits in the production of tool molecules whereby labelling of antibodies with fluorophores or biotin can aid assay development, target identification and beyond.

Often protein labelling for biological assays is achieved by random lysine conjugation using NHS-ester reagents. Recent reports by the groups of Vijay Chudasama and James Baker have shown promising results in the specific conjugation of 4 small molecule payloads to an antibody by di-sulfide bond re-bridging.[3]



At GSK, we have been interested in evaluating antibody conjugation methodologies with a view to protein labelling and ultimately the development of 'next generation' therapeutics. We have prepared novel protein labelling molecules and used these to produce biotinylated biomolecules with a specific loading at defined locations on the protein. Further studies have explored the human serum stability of these conjugates and their application in assay development.

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POSTERS

Challenges and Opportunities in Fragment Based Drug Discovery

RATIONAL DESIGN OF SMALL-MOLECULES INHIBITORS OF HUMAN CYCLOPHILINS WITH A PAN VIRAL ACTIVITIES BY FRAGMENT BASED DRUG DESIGN USING A LINKING STRATEGY

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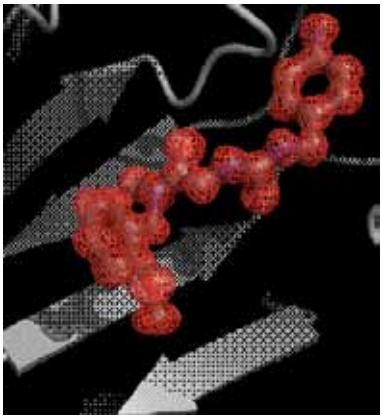

The hepatitis C virus (HCV) is the leading cause of chronic hepatitis, of liver cirrhosis and hepatocellular carcinoma. Roughly 200 millions individuals are infected in the whole world and the infection by HCV causes approximately 280.000 deaths per year. The study of the complex of replication made it possible to highlight the crucial role of cellular partners, in particular the cyclophilins[1], in the driving process with the synthesis of new viral genomes and inhibition of these enzymes lead to new anti-viral agents. The Cyclophilins are enzymes that have been observed abundantly and ubiquitously in a wide range of tissue types and organisms[2,3]. They are characterized by the ability to catalyse the *cis-trans* isomerisation of peptidylprolyl bonds[4] (PPIases) which was identified as the rate-limiting step in protein folding. To design news Cyps inhibitors with low molecular mass, we applied a fragment-based screening approach on Cyclophilin D (CypD). We used X-ray crystallography and NMR that are well adapted to identify weak affinity fragments (mM). We solved 14 crystallographic structures of CypD in complex with fragments (2,00 - 0,97Å). Based on the fragments binding modes, we designed and optimized a new Cyps inhibitors family (proline mimetic). Our lead compound have an IC_{50} of 0,05µM on Cyp *in vitro* and have activities on differents virus (HCV, HIV and coronavirus) on replication *in cellulo*. The presentation will show the used of X-ray crystallography for the discovery of news human Cyps inhibitors using fragment based drug design using a linking strategy[5].

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AGV01-1630, A NEW POTENT AND SELECTIVE ERK INHIBITOR TO TREAT MAPK-DEPENDENT CANCERS

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2) AGV Discovery SAS, Montpellier, France

RAS/RAF/MEK/ERK pathway plays a major role in cell proliferation, growth and survival. This signaling is over-activated in more than 30% of human cancers. Thus, proteins of this MAPK pathway, BRAF and MEK, have been targeted to block tumor growth and have proven clinical efficacy. However, resistance ultimately appears with current targeted therapies(1,2). It now seems essential to develop new therapeutic options to treat MAPK-dependent cancers. Moreover, most resistance to RAF and MEK inhibitors induces ERK reactivation, through different mechanisms such as MEK and NRAS mutations, BRAF and COT amplifications…(3). Therefore, ERK inhibitors may be a method to overcome resistance mechanisms to current RAF and MEK inhibitors. AGV Discovery possesses a potent and selective ERK inhibitor with a strong anti-proliferative activity in a broad range of MAPK-dependent cell lines. This candidate is orally bioavailable and has proven a strong efficacy in a BRAF melanoma xenograft model. AGV Discovery should complete regulatory preclinical studies in 2018 with the aim of launching a first clinical phase for 2018-2019.

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DEVELOPMENT OF SCREENING BIOASSAYS IN THE CONTEXT OF FRAGMENT-BASED DRUG DISCOVERY. A PROOF OF CONCEPT ON THROMBIN

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2) Namur Medicine & Drug Innovation Center (NAMEDIC - NARILIS), University of Namur, Belgium

Fragment-based drug discovery (FBDD) proved its efficacy and gained increasing importance for the research of new drugs in the pharmaceutical industry [1]. FBDD usually starts with the screening of a small library of low molecular weight compounds or fragments against the target of interest. One of the challenges of this approach comes from the necessity of particular techniques to detect fragment binding. Indeed, the use of small fragments for the screening comes at a price, the interactions with the target being very weak (10-1000 μM). Biophysical techniques including NMR methods, X-ray screening and surface plasmon resonance (SPR) is generally the most popular approaches reported in the literature.

In this communication, we will report the development of novel bioassays based on capillary electrophoresis and mass spectrometry. In an **optimized direct ACE method**, we were able to measure and characterize, under physiological conditions, biomolecular interactions between fragments and thrombin (THR) [2]. This method has been designed to screen positively charged fragments at physiological pH. To broaden the scope of this ACE methodology, we currently develop a **competitive ACE-binding assay** with a probe ligand. This makes the assay compatible with all ligands whatever their ionization state and mobilities and thus makes this approach more widely applicable. An alternative approach, we investigate is the **affinity-mass spectrometry (AMS) methodology**. Comparatively to the direct ACE method, mass spectrometry offers the possibility to identify binders among mixtures. Over the last decade, mass spectrometry (MS) has proved to be a promising technique for the screening of ligands and several distinct affinity selection-MS approaches towards screening of bioactives have been developed [3]. We choose size-exclusion chromatography coupled to mass spectrometry (SEC-MS). This method combines a chromatography size exclusion step to separate the enzyme-ligand complex from the free ligand and a MS detection step to identify the ligand bound to the complex.

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THE DESIGN OF NON-PEPTIDIC COVALENT INHIBITORS OF THE IMMUNOPROTEASOME

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The proteasome is an intracellular protease that represents a vital part of the ubiquitin-proteasome system. It degrades many proteins and has critical functions in several biological processes. The constitutive isoform (cCP) of the proteasome is expressed in all eukaryotic cells while its immunomodulatory isoform, the immunoproteasome (iCP) is mainly expressed in cells associated with the immune system. Notably, the expression of the iCP can be induced in non-immune tissues by pro-inflammatory cytokines. Dysregulation of the proteasomes is known to lead to the development of diverse diseases, such as malignancies, autoimmune and inflammatory diseases. The research shows that selective inhibition of the iCP has great potential as a novel approach for the treatment of inflammatory diseases and a wide range of autoimmune disorders [1]. So far, the known inhibitors of the iCP encompass compounds of peptidic type that are prone to poor metabolic stability and low bioavailability [2].

In our research, we are focusing on the identification and development of non-peptidic compounds of both non-covalent and covalent nature that selectively inhibit the chymotrypsin-like (β5i) subunit of the iCP. Molecules of this type have several advantages; besides better stability it is also possible to cover greater chemical and property space, providing more medicinal chemistry options during their optimization. As our initial approach to develop non-peptidic inhibitors, we used virtual-screening and subsequent chemical optimization. Biochemical evaluation of reversibly and irreversibly acting compounds showed that these non-peptidic molecules selectively block the β5i subunit of the human iCP on cell lysates and on intact cells [3]. Our current efforts are devoted to further improvements of the described non-peptidic inhibitors of the iCP by using scaffold morphing and scaffold hopping approaches, as well as to discovering new non-peptidic scaffolds and electrophilic warheads via screening of libraries of both non-covalent fragments and electrophilic warheads (Figure).

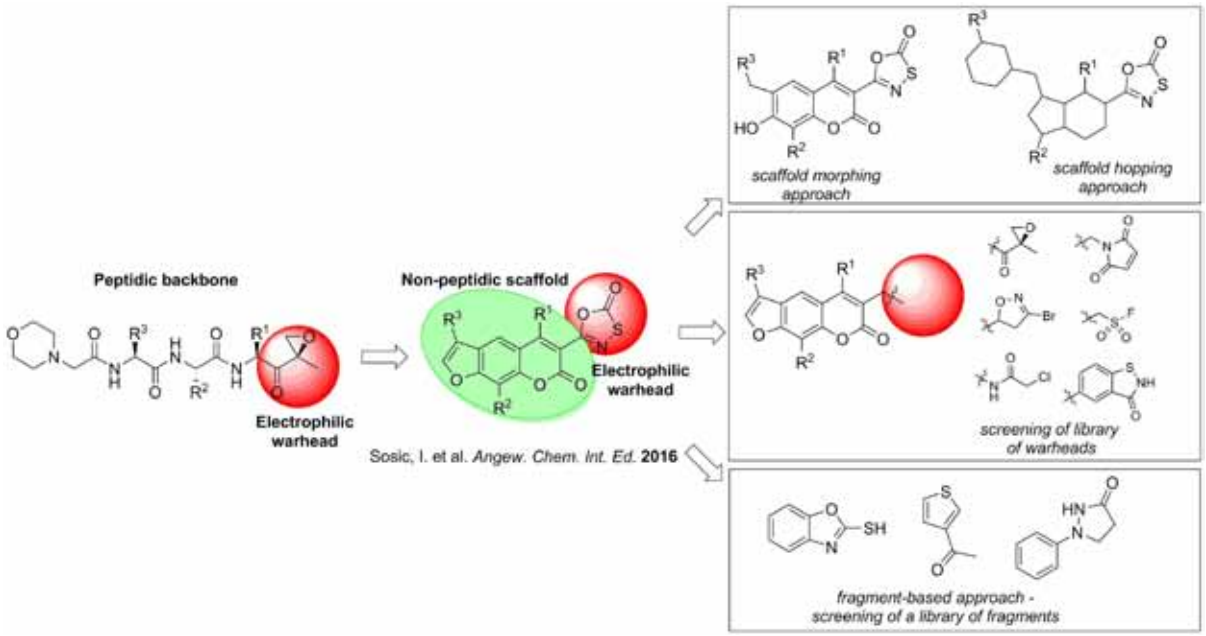

Figure. Schematic representation of the development of non-peptidic inhibitors of the iCP.

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DE NOVO MOLECULAR DESIGN - WHERE NO MEDICINAL CHEMIST HAS GONE BEFORE

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The quest for finding novel chemical entities within an acceptable property space is one where the odds are very much against us: with the druglike chemical universe being estimated to contain ~1060 molecules, the problem closely resembles looking for a needle in a - virtually endless - haystack. Fragment-based approaches can assist us in narrowing down this vast search space, but processing the remaining number of compounds still requires special cheminformatics tools.
In the current study, we are presenting a molecular de novo design workflow where we exploited ultrafast similarity and substructure search solutions (via MadFast Similarity Search and JChem PostgreSQL Cartridge, respectively) in order to find novel compounds with chemical structures, similar to those of known drug molecules. These solutions enabled us to overcome the traditional boundaries of chemical structure searches: we successfully identified close analogues of known drug molecules in the exhaustively enumerated compound set of GDB-13, and performed a systematic intellectual property (IP) check in the SureChEMBL database. These large-volume search actions were followed by clustering in order to determine diverse subsets within the complete list of novel analogues. Other post-filtering actions were also applied, so that the selected compounds could be further characterized based on their 3D- and pharmacophore properties, as well as their synthetic feasibility.
Our work demonstrates that even extremely large compound collections can serve as starting points for finding promising and accessible ligands within the patent-free space. We created this example in the form of a flexible KNIME workflow, so that its steps could be easily modified or expanded with additional filters.

POSTERS

Chemical Biology in Drug and Target Discovery

MOLECULAR DOCKING AND MULTIVARIATE STATISTICAL ANALYSIS AS TOOLS FOR STRUCTURAL OPTIMIZATION OF ANTILEISHMANIAL 2-PHENYL-2,3-DIHYDROBENZOFURANS

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Leishmaniasis is a parasitic tropical disease which affects millions of people around the world, mainly in vulnerable zones in Asia, Africa and America. Although different efforts have been made, there is no any effective treatment so far [1]. Therefore, and continuing with the search for potent and selective antileishmanial agents, a set of 2-phenyl-2,3-dihydrobenzofurans were synthesized by oxidative coupling of substituted phenylacrylates. Evaluation *in vitro* against *Leishmania donovani* amastigotes confirmed their antileishmanial potential as it has been previously reported for this kind of compounds [2]. Some important structural features could be defined as key for their activity and selectivity.

The structures of the synthesized compounds along with several hypothetical analogues were docked on 10 different reported crystal structures of *L. donovani* proteins, including *N*-myristoyl transferase, pteridine reductase I and dihydroorotate dehydrogenase as possible molecular targets. The resulting docking scores were statistically compared and correlated among them and with the actual activity using multivariate tools, including principal component analysis, hierarchical clustering analysis and partial least squares. Good linear correlation between antileishmanial activity and docking scores was found, allowing further prediction of more potent compounds from simple docking calculations. The synthesis of the predicted compounds as well as some other analogues to widen the model is currently ongoing. Validation of the inhibition of the key proteins by the synthesized 2-phenyl-2,3-dihydrobenzofurans is still required.

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MESOIONICS TALES: FROM A NEW BIO-ORTHOGONAL REACTIVITY TO "CLICK AND RELEASE" LINKERS

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The discovery and exploration of bio-orthogonal reactions for the specific labeling of biological entities is a major challenge. To date, a variety of bio-orthogonal reactions have been described, including the Inverse Electron Demand Diels-Alder (IEDDA) reaction between strained alkynes or alkenes and tetrazines and the Strain Promoted Azide-Alkyne Cycloaddition (SPAAC). These "click" reactions are the most popular for *in vivo* or *in vitro* chemical modifications of biomolecules.[1-3]

Our group have identified a new copper-catalyzed reaction coined (CuSAC) involving sydnones, a notable member of mesoionic dipoles, and a terminal cycloalkynes leading to the formation of a pyrazole cycloadducts[4]. Sydnones are also exquisite partners for Strain Promoted Sydnone-Alkyne Cycloaddition (SPSAC) with cycloalkynes. Both CuSAC and SPSAC ligations proved to be tolerant towards complex biological media.[5]

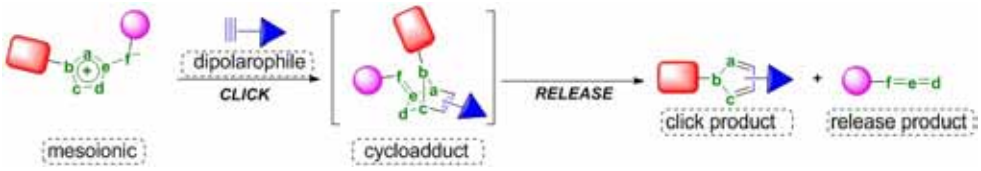

Figure 1: Target reaction for the screening

During the formation of the desired pyrazole unit a concomitant extrusion of a stoichiometric amount of carbon dioxide (CO_2) takes place. Realizing the potential of such a release process, we decided to explore its generality by identifying new "*click* and *release*" reactions involving mesoionics with strained cyloalkynes, through LC-MS screening of a library of 25 mesoionics (Figure 1).

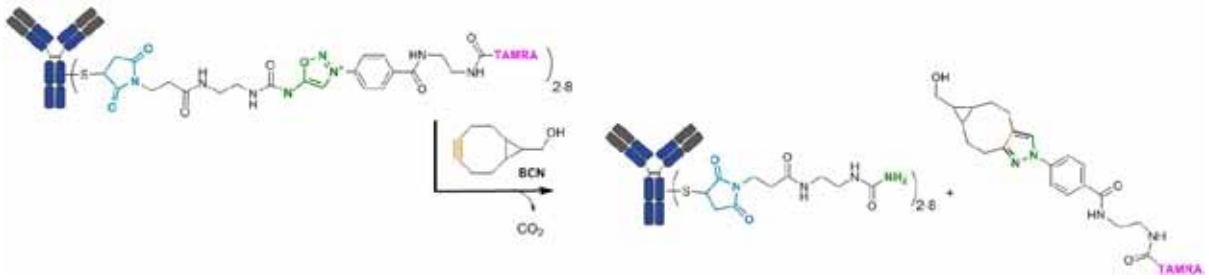

Figure 2: Proof of concept of ADC cleavable linkers

The screening identified an unprecedented strained promoted cycloaddition reaction with imino-sydnone. Optimized imino-sydnones were successfully used to design innovative cleavable linkers suitable for protein modifications, opening new areas in the fields of drug release (Figure 2) and target fishing applications. [6, 7] This new technology will have major impact in the design of Antibody-Drug Conjugate (ADC) and trans-tagging modifications.

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NEW HYDRAZONES CONTAINING 1,4-PHENYLENE-BISTHIAZOLE SCAFFOLD: SYNTHESIS, ANTI-CANDIDA EVALUATION AND MOLECULAR DOCKING STUDY

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Different *Candida* strains, including *C. albicans*, *C. krusei* and *C. parapsilosis* are responsible for life-threatening infections in humans. The widespread incidence of multi-drug resistant infections caused by these *Candida* species and the high rate of mortality associated with these infections, revealed that current therapeutic options available to treat candidiasis are ineffective or insufficient (1, 2).

In the present work, new hydrazones containing 1,4-phenylene-bisthiazole moiety were synthesized and evaluated as anti-*Candida* agents. The structure of the newly synthesized compounds was confirmed by elemental analysis and IR, MS, ^{1}H-NMR and ^{13}C-NMR spectroscopic methods.

The anti-*Candida* activity of the new compounds was investigated using an *in vitro* broth microdilution test, against four different *Candida* strains. Results showed that some of the tested compounds had an anti-*Candida* activity equal to the one of fluconazole, the most frequently antifungal drug used.

Moreover, an *in silico* molecular docking study was performed, in order to predict a possible mechanism of action of these compounds. This study revealed that there is a strong interaction between our tested compounds and fungal lanosterol 14α-demethylase.

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OAT-2068 - THE FIRST SELECTIVE INHIBITOR OF MOUSE CHITOTRIOSIDASE (mCHIT1)

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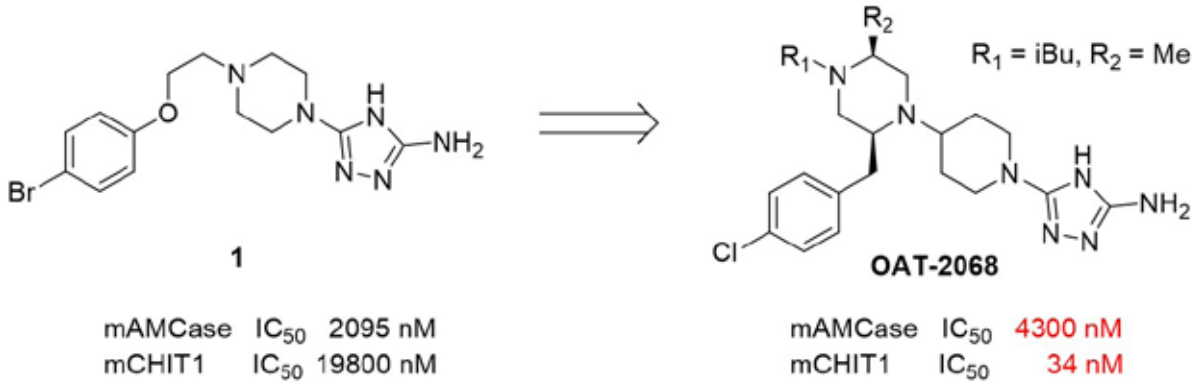
Chitotriosidase (CHIT1) is a 52-kDa protein belonging to the GH18 glycoside hydrolases family and is one of the two enzymatically active chitinases in mammals (acidic mammalian chitinase - AMCase is the other one). It contains a GH18 catalytic domain linked by a hinge to a chitin-binding domain and it catalyzes hydrolysis of the β-(1,4) glycosidic bond between N-acetylglucosamines in the chitin chain. Increased CHIT1 activity is an established biomarker of Gaucher's disease. Elevated CHIT1 levels and activity were also found in the plasma and bronchoalveolar lavage (BAL) fluid from patients with various lung pathologies including interstitial lung diseases, such as idiopathic pulmonary fibrosis and sarcoidosis, as well as in chronic obstructive lung disease and asthma [1].

Herein we report the structure-based optimization of compound **1**[2] that led us to discovery of several novel highly potent inhibitors of CHIT1. Among them OAT-2068 displays a remarkable 143-fold mCHIT1 vs. mAMCase selectivity.



In vitro structure-activity relationship data, synthesis, pharmacokinetic properties of selected compounds will be presented. OAT-2068 represents a highly potent and the most selective inhibitor of mCHIT1 described to date. These characteristics together with excellent pharmacokinetic profile, make it an ideal tool compound to study the role of CHIT1 in biological systems, including animal models of human diseases.

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IN CELL TARGET OCCUPANCY AND VISUALIZATION OF SMALL MOLECULAR PROBES

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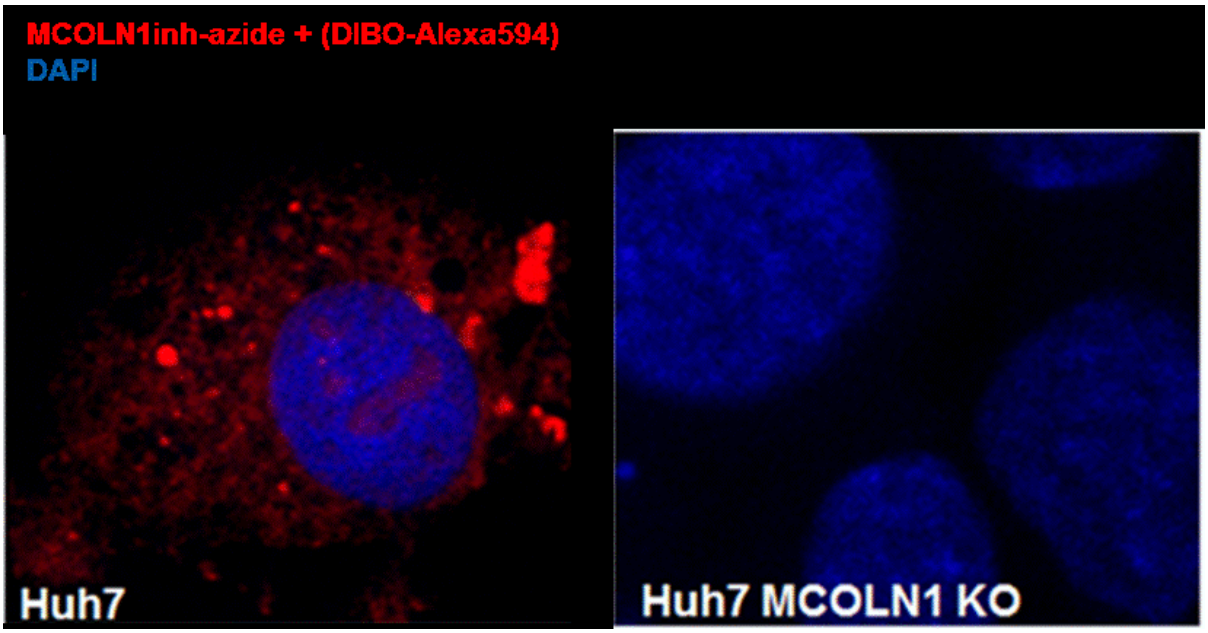
*An attempt at visualizing the Fourth Dimension: Take a point, stretch it into a line, curl it into a circle, twist it into a sphere, and punch through the sphere.*Albert Einstein

The visualization and monitoring of specific proteins without disturbing their biological function is a major challenge in chemical biology. For decades many of the proteins that drive diseases have evaded drug hunters that we are and as such deciphering how small molecule modulators bind their intracellular targets is a fundamental and daunting task. In order to increase our understanding of targeted pharmacological mechanisms, we have been designing, engineering and further validating a set of small molecular probes that were successfully labeled and visualize while engaged in their specific target.

Herein, we report for the first time a small selection of fluorescent reporters than can be site-specifically incorporated and utilized to visualize target occupancy to proteins of interest in mammalian cells. This approach is now suitable to a variety of key targets (*i.e.* E2F1, MCOLN1, adrenergic receptor, LGR4, ER…) with important lead discovery applications.



PROTEOME-WIDE DETERMINATION OF COVALENT AND NON-COVALENT TARGETS OF A SELECTIVE IRREVERSIBLE PI3Kδ INHIBITOR

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The classical method to achieve irreversible kinase inhibition is to bind to poorly conserved, weakly nucleophilic cysteine residues using Michael acceptors. Multiple kinases have been targeted successfully using this approach, however it is to date limited to ~200 of ~500 proteins that possess such a cysteine residue in the ATP active site.[1] Previously, we disclosed the discovery of a selective, irreversible inhibitor of PI3Kδ (named 1) that challenged this established trend by reacting specifically with the ATP-binding lysine.[2] This residue is conserved throughout the kinome, yet this compound showed excellent selectivity over a selection of lipid and protein kinases in biochemical assays. This poster builds on this work, reporting the design, synthesis, and biological characterisation of a clickable analogue of 1 that was used to identify covalent and non-covalent targets in live cells. We first confirmed target engagement in complex cell-lysates using strain-promoted azide-alkyne cycloaddition chemistry with a fluorescent handle, coupled to SDS-PAGE separation and in-gel fluorescence detection. Then, utilising quantitative chemoproteomics in Ramos cells, we showed that small molecule inhibitor 1 covalently competed the binding of the azide probe to handful of specifically enriched proteins. Dose-response curves generated for the covalent targets in the proteomic study demonstrated that the highest affinity was achieved for our kinase of interest, PI3Kδ (>30-fold selective). This work underscores the orthogonality of this method to traditional cysteine targeting for generating selective irreversible kinase inhibitors, and is anticipated to be applicable across the kinome. Furthermore, this work also supports the emerging concept of lysine-targeting for covalent inhibitor development, adding to the chemical biology and drug discovery tool box.

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LEVERAGING RESISTANCE TO DESIGN SELECTIVE AND POTENT CHEMICAL PROBES FOR PROTEINS IN THE AAA+ FAMILY

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Recent methodological advances have accelerated the discovery of chemical probes for studying biological processes. However, developing selective probes remains challenging if there is a lack of robust structural models for how the compound and the target protein may interact, especially when structural similarity in the compound-binding site increases the likelihood of off-target effects. Here, we focus on AAA+ ATPases, a large enzyme superfamily (~100 in humans) for which selective chemical inhibitors with defined mechanism-of-action are remarkably scarce. We describe an approach in which single amino acid variances in the conserved active site of AAA+ proteins are leveraged to engineer silent mutations exploitable for selective inhibitor design. We used this approach to rationally develop a selective chemical probe for spastin, a AAA+ microtubule-severing enzyme implicated in neurodegeneration. Furthermore, by comparing dose-dependent phenotypes in isogenic cells carrying either a sensitive or inhibitor-resistant allele of spastin, we examined the role of spastin, without interference from potential off-target effects, in the microtubule cytoskeleton during cell division. Our results suggest a general strategy for streamlining target-based approaches in drug discovery by exploiting rationally designed resistance-conferring mutations.

DAPTOMYCIN, A LAST-RESORT ANTIBIOTIC, BINDS RIBOSOMAL PROTEIN S19 IN HUMANS

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Daptomycin (DAP) is a recently introduced, last-resort antibiotic that displays a unique mode of action against Gram positive bacteria that is not fully understood. Several bacterial targets have been proposed but no human binding partner is known.

In the present study [1] we tested DAP in cell viability and proliferation assays against six human cell lines, describe the synthesis of biotinylated and fluorescently labeled analogues of DAP. Biotinylated daptomycin was used as bait to isolate the human binding partner by the application of reverse chemical proteomics using T7 phage display of five human tumor cDNA libraries. The interaction between the rescued protein and DAP was validated via siRNA knowdown, DARTS assay and immunocytometry.

We have found that daptomycin possesses selective growth inhibition of some cancer cell lines, especially MCF7. The unbiased interrogation of human cDNA libraries, displayed on bacteriophage T7, revealed a single human target of DAP; ribosomal protein S19 (RPS19). Using a drug affinity responsive target stability (DARTS) assay in vitro, we show that DAP stabilizes RPS19 toward pronase (Fig. 1). Fluorescently labeled daptomycin stained specific structures in HeLa cells and co-localized with a RPS19 antibody (Fig. 2).

This study provides, for the first time, a human protein target of daptomycin and identifies RPS19 as a possible anticancer drug target for the development of new pharmacological applications and research.

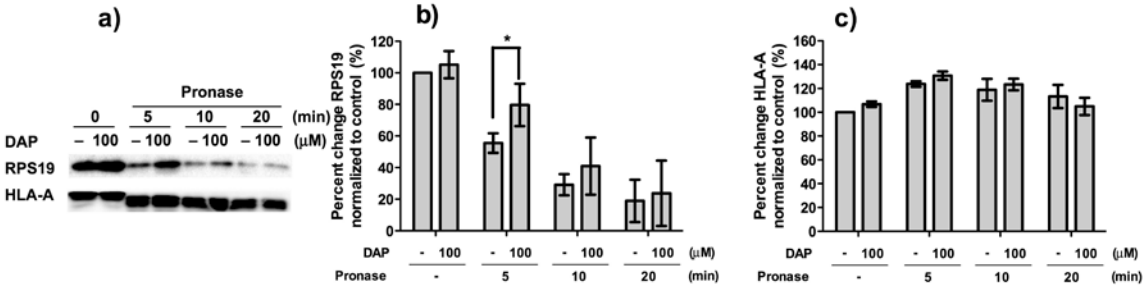

Fig. 1. Validation of the binding of DAP to RPS19 *in vitro* and *in vivo*. a) Western blotting of DARTS analysis in respect with RPS19 and HLA-A (loading control) in DAP and pronase treatment. b) graphical representation of a) for RPS19 run in triplicate. * designates $p < 0.05$. c) graphical representation of a) for HLA-A run in duplicate.

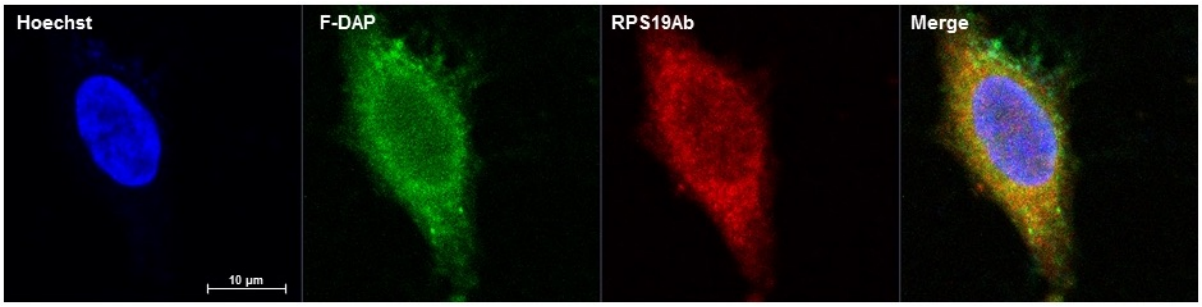

Fig. 2. Confocal images of HeLa cells. Hoechst 33342 (blue), F-DAP (green) and RPS19Ab (red), colocalization (orange).

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ARTESUNATE TARGETS THE HUMAN BCL-2 ANTAGONIST OF CELL DEATH PROMOTER

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Artemisinins are sesquiterpene lactones extracted from sweet wormwood (*Artemisia annua*) and constitute the most potent and safe antimalarials currently available. They also have selective anticancer activity, yet despite their clinical potential, no human target of the artemisinins is known and their mode of action still unclear [1]. In parallel to their antimalarial activity, it is widely believed that the endoperoxide bridge in artemisinins initiates oxidative stress in cancer cells through formation of reactive oxygen species (ROS), which leads to apoptosis [1,2]. Other evidence points to necroptosis or ferroptosis as modes of action.

Starting from artemisinin, we synthesised biotinylated and fluorescently labelled version of artesunate (ART) (Fig. 1). Biotinylated artesunate was used as bait to interrogate several human cancer cDNA libraries, displayed on the surface of bacteriophage T7. After several rounds of biopanning, we identified a single human target of ART; the Bcl-2 antagonist of cell death promoter (BAD) (Fig. 1). Fluorescently labelled artesunate was shown to colocalise with BAD antibody in HeLa cells and that the cytotoxicity of ART was abrogated by knocking down BAD with siRNA. We show that ART interacts with BAD in HeLa cells and inhibits the phosphorylation of BAD, thereby promoting the formation of the proapoptotic BAD/Bcl-xL complex and the subsequent intrinsic apoptotic cascade resulting in cell death. This unanticipated role of BAD as a target of ART points to new avenues for clinical exploitation of artemisinins in the Bcl-xL life/death switch.

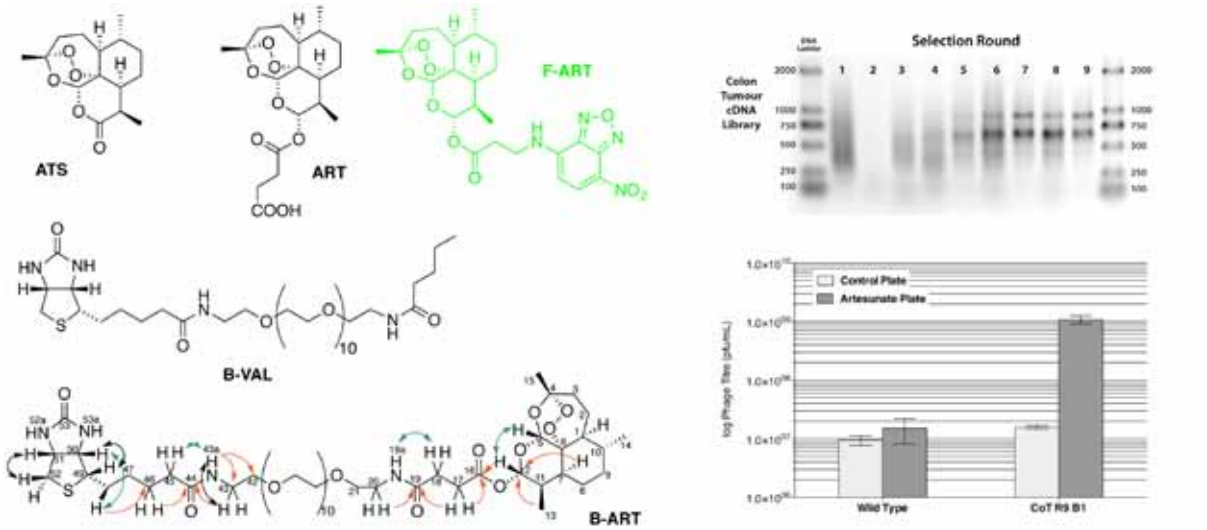

Fig. 1. (***left***) Structures of artemisinin (ATS), artesunate (ART), biotinylated ART (B-ART) and fluorescent ART (F-ART) and control probe biotinylated valeric acid (B-VAL). BAD identified as a common protein binding partner of ART by phage display using 5 cDNA libraries from various cancer cells. (***top right***) Agarose gel electrophoresis of phage DNA inserts amplified by PCR from phage sub-libraries after nine rounds of selection with biotinylated artesunate (B-ART) immobilised on neutravidin-coated microtitre plates. (***right***) On-phage binding study showing 100 fold stronger affinity of the BAD-displaying phage clones for the ART-immobilised support, than for the support with immobilized negative control, B-VAL. The wild-type phage clone without a displayed protein does not differentiate the two supports with B-ART or B-VAL.

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PHENOTYPIC SCREENING COMBINED TO DRUG TARGET IDENTIFICATION IDENTIFIES NOVEL MODULATORS OF BETA-CELL REGENERATION

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Understanding how a bioactive molecule works is essential in many aspects of life sciences and specifically in the drug discovery and development cycle. Projects initiated via phenotypic screening approaches need target deconvolution methods to progress more efficiently.

We have developed ULTImate YChemH, a powerful chemical biology tool to identify the direct protein targets of small molecules. It is a unique screening platform based on an improved Chemical Yeast Three-Hybrid technique. Highly complex protein domain libraries, prepared from any cell type or tissue, are screened to saturation to identify partners and their interacting domains using a transcriptional read-out. Sophisticated bioinformatics analysis allows to attribute confidence scores to each interaction. This in-yeast screening technology has been optimized for small molecules with a special emphasis on chemical derivatization and the generation of permeable yeast strains. Our versatile ULTImate YChemH technique is complementary to other proteomics technologies, with several key advantages: it is an unbiased, *in vivo* screening technology as it screens the entire proteome from a given tissue or cell line. The absence of any washing steps contributes to its high sensitivity. In addition, each putative interaction partner is tested individually, eliminating the competition by abundant or strong binders.

With the overarching goal of developing new therapies for diabetes, an unbiased chemical-genetic screens in zebrafish was performed to identify compounds, signals and cellular mechanisms that promote beta-cell regeneration. Hit compounds were selected for optimization and targets deconvolution. Ultimate YChemH was used for identifying targets of the most potent hit compound. It resulted in a short-list of 3 top candidate targets, out of which one was confirmed to directly interact with the compound using surface plasmon resonance. A chemically divert inhibitor of the target protein displayed similar biological effects as our hit, adding confidence to the proposed target and the screening rationale.

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TOWARDS THE DEVELOPMENT OF A SCALABLE IPSC CULTURE USING SMALL MOLECULE DISRUPTERS OF CELL-CELL ADHESION

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Pluripotent stem cells can be maintained in an undifferentiated state and have the ability to transform into almost all cells of the adult human body, thus they provide an excellent platform to study human disease mechanisms, develop regenerative therapies and screen molecules for drug discovery projects. Recent advances in cell culturing technology have provided a means with which to generate induced pluripotent stem cells (iPSCs) from mature somatic cells.[1] Traditionally, two dimensional systems are utilised for the culturing of iPSCs, which require cell-matrix interactions in order to maintain both the pluripotency and viability of the cells.[2,3] However, such approaches are disadvantaged by their inability to produce iPSCs on a sufficient scale. Attempts to improve scalability by using 3D suspension cultures have so far met limited success.[4] One issue relates to the tendency of iPS cells to form tight aggregates which can prevent the inner cell mass from being exposed to the culture medium and lead to unintended differentiation or cell death. Methods to prevent such aggregation (e.g. physical agitation) often lead to reduced cell viability or loss of their pluripotent state, and limitations on cell density are generally encountered. Accordingly, the discovery of new methods to allow a reliable, cost effective large scale production of iPSCs is highly desirable.

Recently, our group has focused on establishing a possible method to develop a single-cell suspension culture of iPS cells that could occur through the disruption of one of the key cell-cell adhesion molecules, the transmembrane E-cadherin protein.[5] Following a small molecule screen, the natural product (-)-indolactam V (ILV) was discovered to reversibly induce a morphological change in iPSCs in which the cells disaggregate via an apparent PKC-mediated disruption of cell-cell adhesion. Crucially, these contact-independent cells appear to retain both viability and pluripotency after multiple passages with no spontaneous differentiation occurring. Further investigation into PKC isoform-selective analogues of ILV identified compounds which exhibit improved cell viability within 2D culture compared to ILV treatment. Further applications of these disruptive chemical tools in the scale up of iPSCs in 3D culture are currently being investigated and recent research in this area will be presented.

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SYNTHESIS OF SOME NEW THIAZOLIDINE-2,4-DIONE DERIVATIVES AS POTENTIAL ANTI-CANDIDA AGENTS

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Infections in the immune-compromised patients with resistant fungal strains are nowadays a big challenge of treatment in all health care systems worldwide. It represents one of the most life-threatening complications with a poor prognosis. For example, the commensal *Candida sp.* is common in humans, but frequent became dangerous pathogen (1). It is imperative that new molecules with putative antifungal properties to be found. This approach came in order to avoid their achieved resistance. Inhibitors with different mechanism than classic antifungals could be developed based on *in silico* techniques. Molecular modelling and ADMET can be used in order to develop more potent compounds at lower doses, with less toxicity and with better pharmacokinetics (2).

Thiazolidine-2,4-dione derivatives were synthesized under microwave irradiation. First, the Knoevenagel condensation in position 5 of the thiazolidine-2,4-dione ring was performed using various phenolic aldehydes. Further, nitrogen and oxygen atoms of the intermediate compounds were substituted using various halogenated compounds. The purity of the new synthesized thiazolidine-2,4-dione derivatives was confirmed by thin layer chromatography and liquid chromatography. The structure of the new compounds was confirmed by spectral analysis: infrared spectroscopy, mass spectrometry, ^{1}H NMR and by quantitative elemental analysis.

Compounds were screened *in vitro* for their ability to inhibit the growth of some standardized fungal strains. *In silico* evaluations were performed in order to find potential interactions of novel molecules to lanosterol 14α-demethylase using AutoDock 4.2 (3) and an ADMET study using Swiss ADME (4).

Our screening showed that some of the new compounds have promising antifungal activity.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF N6-SUBSTITUTED 2´-DEOXY-9-(β)-D-RIBOFURANOSYLPURINE DERIVATIVES

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Cytokinins are phytohormones playing a key role in the regulation of plant growth and development including seed germination, apical dominance and senescence. Purine cytokinins are adenine or adenosine derivatives with substitution in the position N^6 of the purine scaffold and due to the presence of a side chain they are divided into two main groups: isoprenoid and aromatic. It has been shown that selected cytokinins and cytokinin 9-(*β)* -D-ribosides have important antiproliferative properties against cancer cell lines. In this project we decided to focus on related group of compounds, specifically 2´-deoxy-9-(*β*)-D-ribofuranosylpurine derivatives, in respect to their ribosides‘ anticancer activity. A series of 2´-deoxyriboside derivatives of aromatic cytokinin benzylaminopurine with different benzylamines substituted has been prepared for testing of cytotoxicity and biological activity on *A. thaliana* AHK3 and AHK4 receptors and three cytokinin bioassays (*Amaranthus*, senescence and tobacco callus bioassay) were employed. We discuss differences in antiproliferative activity of cytokinin free bases, ribosides and 2´-deoxyribosides. Furthermore, our interest is particularly in study of ability of novel compounds to regulate plant growth. Additionally, we propose that some of these derivatives can act as potential antivirotic agents.

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DESIGN OF A DIMERIC APTAMER AGAINST B-CELL RECEPTOR

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DNA Aptamers are oligonucleotides that can bind to various target molecules and are useful in biomedical applications. The Systematic Evolution of Ligands by EXponential enrichment (SELEX) is the method used to identify aptamers from a library of single stranded oligonucleotides through enrichment and amplification. A variant of SELEX termed Ligand Guided Selection (LIGS) was introduced from our lab that allows identification of specific aptamers against the cell-surface proteins using whole-cells. Using the LIGS method, DNA aptamer R1 was selected against the membrane bound IgM (mIgM) of the Burkitt's lymphoma cells and its truncated version R1.2 was introduced to improve its affinity. Here, we will describe the systematic design of dimeric versions of R1.2 to enhance the affinity of R1.2 against B cell receptor. Three dimeric aptamers were synthesized using 3, 5 and 7 polyethyleneglycol (PEG) linkers that tether the two aptamers, forming DR1.2.3S, DR1.2.5S and DR1.2.7S respectively. A fluorophore was added to the 5' end of the aptamer to allow detection of the binding aptamers. The analysis of specificity of the dimeric aptamer against panel of B-cell lymphoma and T-cell leukemia revealed that dimeric version retained its specificity while the affinity analysis results revealed that all three dimeric aptamers have a higher affinity than the monomeric version.

SYNTHESIS AND BIOLOGICAL ACTIVITY OF POLYAMINE-BASED ANALOGUES AS POTENTIAL CYCLIN-DEPENDENT KINASE INHIBITORS FOR TARGETED DELIVERY

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Cyclin-dependent kinases (CDKs) belong to a class of protein-kinases that play a well-established role in the control of the eukaryotic cell division and modulation of transcription in the response to several cellular cues. Uncontrolled cell proliferation of tumor cells is often associated with disruption of CDKs' activity, overexpressing of cyclins and also with mutations of genes encoding important proteins involved in the regulation of the cell division. Scientific interest is currently focused on the development of effective cyclin-dependent kinase inhibitors and many of these agents with anti-tumor activity have been included in the clinical studies. Unfortunately, most of them have not been approved due to the presence of adverse drug reactions and low specificity of tumor cells in respect to chemoterapeutics.

The main challenge of our project is to prepare selected cyclin-dependent kinase inhibitors with potential enhanced selectivity against cancer cells mediated by polyamine transport system (PTS). Over the last few years a number of known cytotoxic agents using polyamines as vectors for selective transport to tumor cells have been developed. Natural polyamines (putrescin, spermine and spermidine) are essential for many functions in the cell, including cell proliferation, differentiation and survival. It has been shown that regulating the content of polyamines in the intracellular space is necessary for normal cell growth. Compared to healthy cells, tumor cells have increased accumulation of polyamines due to increased uptake of polyamines from external sources. Upregulation of polyamine transport system in tumor cells is a pivotal factor for the use of polyamines as vectors for the selective transport of cytotoxic chemotherapeutics. However, the most important for transport of polyamine conjugates is an accomplishment of structural requirements of PTS.

In an effort to develop selective substances for tumor cells that would block the cell cycle and induce apoptosis, we are focused on the synthesis and biological activity of cyclin-dependent kinase inhibitors based on 2,6,9-trisubstituted purine scaffold conjugated with polyamines. The selective delivery of prepared derivatives in cancer cells via the PTS will be validated with two parental and mutated ovarian *cell line* models (CHO and CHO-MG) to compare whether these compounds preferentially use the PTS to access cells.

This project is supported by IGA_PrF_2017_010 and GA ČR 15-15264S grants.

IDENTIFICATION OF HIV LATENCY REACTIVATION AGENTS THROUGH PHENOTYPIC SCREENING

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Recent advances in the fields of biology, chemistry, proteomics and screening technology have greatly improved our chances of identifying underlying protein targets. We will describe progress on all these fronts as they relate to the discovery of mechanisms and chemical matter, derived from a ultra-high throughput phenotypic screen, which induce latent HIV expression in infected cells. In particular, we will describe the identification of new chemical matter for HIV reactivation and identification of a proposed mechanism of action via pull-down experiments, biophysical and structural confirmation, and subsequent mechanistic experiments to understand differences between biochemical and cellular results.

POSTERS

Drug Discovery Tales

DISCOVERY OF PRONEUROGENIC DRUG CANDIDATES: A NEW THERAPEUTIC STRATEGY FOR NEURODEGENERATIVE DISORDERS

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Neurodegenerative diseases exert a vast physical, emotional and economic cost on patients and society, and with an aging population their prevalence is rapidly increasing. There are currently estimated to be 47m people living with dementia globally, costing over $800b each year, but this is predicted to rise nearly three-fold by 2050.[1] The only treatments currently available for these conditions are symptomatic, with none targeting underlying causes; thus there is an enormous unmet medical need.

We aim to activate neuroregeneration by targeting the endogenous neural stem cells (NSCs) already present within the adult brain and stimulating natural repair mechanisms. This could be utilised as a novel treatment for a range of conditions including Alzheimer's disease, Parkinson's disease and traumatic brain injury. NSCs are found within two main neurogenic niches; the subgranular zone (SGZ) of the hippocampal dentate gyrus, and the subventricular zone (SVZ) of the lateral ventricles. These cells are known to become activated upon injury, and their progeny to then migrate toward the damaged area, but only to a very limited extent. Enhancement of this process has been observed during treatment with a range of drugs, molecules and genetic manipulations, this provides precedent that our approach is feasible.[2]

We have developed a semi-automated *in vitro* phenotypic assay, using a monolayer of primary murine NSCs (isolated from SGZ or SVZ) and measuring the appearance of mature neurons. We have used this assay to perform a pilot screen of 1500 compounds, from which we identified 30 compounds which induced a significant increases in neurogenesis. The use of a phenotypic assay gives us the opportunity to utilise a hypothesis-free and target agnostic approach, whilst also allowing a more direct translation of results into *in vivo* studies. Following preliminary pharmacokinetic evaluation, early *in vivo* efficacy work was conducted, wherein one lead compound was found to give a significant enhancement in SGZ neurogenesis after oral administration to wild-type mice. As a result, this compound has now been progressed to Alzheimer's disease models. Work is ongoing to optimise the ADME / PK and efficacy properties of this and other series, and in parallel to identify and study their mechanism(s) of action.

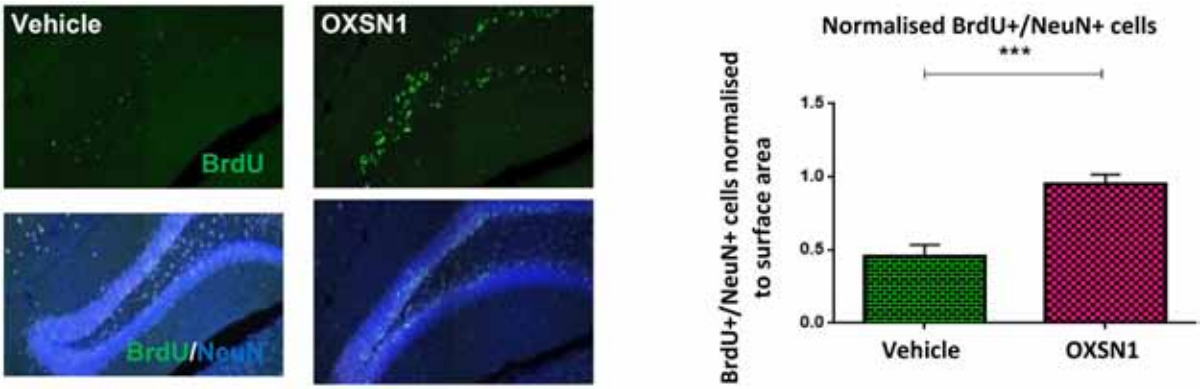

Figure 1. (left) Sections of the anterior DG after treatment with vehicle or OXSN1, stained for BrdU or BrdU/NeuN. (right) Graph showing the normalised number of BrdU+/NeuN+ cells after treatment with vehicle or OXSN1.

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INHIBITION OF SERINE PROTEASE BY GEMINOID PEPTIDE AMPHIPHILES

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Flaviviridae mosquito-borne diseases are an increasing health concern, affecting about half of the whole human population, living in the tropical region of the world.[1] Dengue and Zika are clinical targets with an urgent and unmet need of a therapeutic agent, given the intrinsic difficulties in the development of a vaccine for such illnesses. In fact, four serotypes of Dengue are known, and immunization to one serotype result in an increased risk of contracting the fatal hemorrhagic fever, once infected a second time by another serotype, due to an antibody-dependent enhancement of the disease.[2]

Herein we report the discovery[3] of novel geminoid amphiphilic lipopeptides able to arrest the viral growth through inhibition of the viral protease NS2b/NS3.This is a serine protease, expressed in the viral polyprotein, whose sequence is mostly conserved amongst the four serotypes and partially in Zika and other Flaviviridal agents; it is a key machinery to allow viral maturation: NS2b/NS3 cleaves the viral polyprotein releasing the components of the new virions.[4]

The geminoids here described consist of a peptide with hydrophobic tails at both ends. In this work, a library of geminoids was synthetized, with modifications of the amino acids and the length of the hydrophobic tails. The obtained compounds were screened against a number of proteases. The compounds showing both protease inhibition and selectivity towards viral targets over endogenous proteases were tested in a replicon assay[5] and viability tests, to determine EC_{50}, IC_{50}, and a preliminary cytotoxicity.

The most promising compound was tested on a Dengue virus replication assay and toxicity assay on Vero cells, showing effective inhibition of Dengue virus replication, dependent on concentration of the inhibitor and initial viral load. We will discuss results and implications for drug discovery for Dengue antivirals.

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A SMALL MOLECULE APPROACH FOR THE IN SITU MANIPULATION OF STEM CELLS AS A THERAPEUTIC STRATEGY

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The ability to harness adult stem cells for the treatment of human disease could revolutionise the field of medical therapeutics. They are remarkable cells characterised by their capacity to divide and to differentiate into cell types constituting adult tissue in the body. Moreover, many examples are now described where these cells contribute to tissue repair in the event of injury. Such cells thus hold enormous promise both for use as *in vitro* screening tools for drug efficacy and toxicity testing, but especially for their application in regenerative therapies treating a wide range of disorders with high unmet medical need such as neurodegenerative diseases, diabetes, heart disease, and vision loss.[1,2]

Currently, most regenerative medicine therapies are based on manipulation of stem cells *in vitro* followed by transplantation into the patient. Our approach is to stimulate the adult stem and precursor cells with small molecules *in situ*, taking advantage of the endogenous repair mechanisms that already exist within the body. This would have several advantages, such as avoiding manufacturing of cells *in vitro*. We are using phenotypic high throughput screens based on cultures of tissue-specific cells to identify and optimise new classes of compounds with novel mechanisms of action.

In the first instance, we are applying this unique approach to a number of debilitating conditions with significant unmet medicinal need across several therapeutic areas. OxStem Neuro are identifying new classes of drug that stimulate *de novo* neuron production from neural stem cells that can compensate for disease pathology in neurodegenerative diseases and restore cognitive function; OxStem Cardio aims to stimulate resident cardiac precursor cells using small molecules to increase cardiac muscle regeneration and improve functional recovery following myocardial infarction (MI); OxStem Ocular is working on the stimulation of appropriate precursor cells within the retina of patients with a range of retinopathies to activate retinal repair to restore vision. This poster will highlight the cutting-edge approach of our work in this field, displaying an overview of each of the four areas, with specific focus on the oncology project.

In Oncology, we are targeting the manipulation of 'Cancer stem-like cells' (CSCLs) for the development of novel cancer therapeutics. CSCls are tumorigenic cells that have the ability to self-renew and differentiate to grow and replenish the bulk tumour. The resistance of CSLCs to cytotoxic chemotherapy regimens, characterised in a range of cancer types, is a key reason for the high rates of relapse and remission seen in numerous cancers. This is very evident in Acute Myeloid Leukemia (AML), a cancer of the haematopoietic system, resulting in a long-term survival rate of only 20-30%. Our aim is to use a small molecule approach to induce differentiation of CSLCs to more benign states to improve clinical outcomes and prevent resistance/relapse. With this goal in mind, we have developed a robust *in vitro* screening assay which has been used to identify a number of validated hit compounds that show differentiation in AML cell lines. A lead generation campaign is currently underway as well as in-depth RNA sequencing experiments to shed light on the target pathways in this process.[3]

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DISCOVERY AND PREPARATION OF RORC2 INVERSE AGONISTS

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The nuclear hormone receptor RORC2 represents a promising target for therapeutic intervention by a small molecule given the biochemical pathway linkage to established clinical efficacy through IL-17 modulation and the opportunity for structure-based design enablement. The identification of a small molecule RORC2 inverse agonist evolving from a screening hit to a potent, selective, and metabolically stable compound exhibiting desirable properties within druglike chemical space will be presented. Careful attention to x-ray crystallography-aided structure-based drug design, along with robust, high-throughput synthetic approaches to complex targets were critical to the evolution of this program and will also be discussed.

NOVEL SELECTIVE MAO-A/B INHIBITORS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

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Monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) are FAD-dependent oxidoreductases catalyzing oxidative deamination of various biogenic and exogenic amines. Both enzymes are validated targets in the therapy of several disorders, e.g. depression, Parkinson's disease.[1] Several studies have confirmed involvement of MAO-A/B in the pathogenesis of Alzheimer's disease and other neurodegenerative disorders, where the activity of the enzyme increases.[2] Pirolidin-2-one moiety of a selective human butyrylcholinesterase (hBChE) inhibitor **1**[3] (Figure 1) was replaced with propargyl moiety in order to impart MAO inhibitory properties,[4] . A series of over 80 derivatives devoid of hBChE activity was synthesized by applying systematic structural modifications on the benzene ring and by replacing piperidine with smaller or bigger saturated rings. Several 1,4-disubstituted derivatives with *trans*-vinyl or ethyl linker connecting piperidine and benzene ring displayed IC_{50} values lower than 100 nM for MAO-B. Crystal structure of 4-fluorobenzen substituted N-propargylpiperidine in complex with human MAO-B was resolved, confirming irreversible covalent inhibition of MAO-B. On the other hand, derivatives with prolonged substituent (butinyl/pentinyl) on piperidine nitrogen displayed reversible inhibition of MAO-B, as demonstrated by 100-fold dilution assay. Interestingly, *cis* isomers with smaller substituents (e.g. fluorine) on the benzene ring are selective irreversible MAO-A inhibitors with nanomolar affinity. Both series of compounds are not cytotoxic to neuroblastoma SH-SY5Y cell line and display neuroprotective properties in the cell based 6-OHDA model of Parkinson's disease.

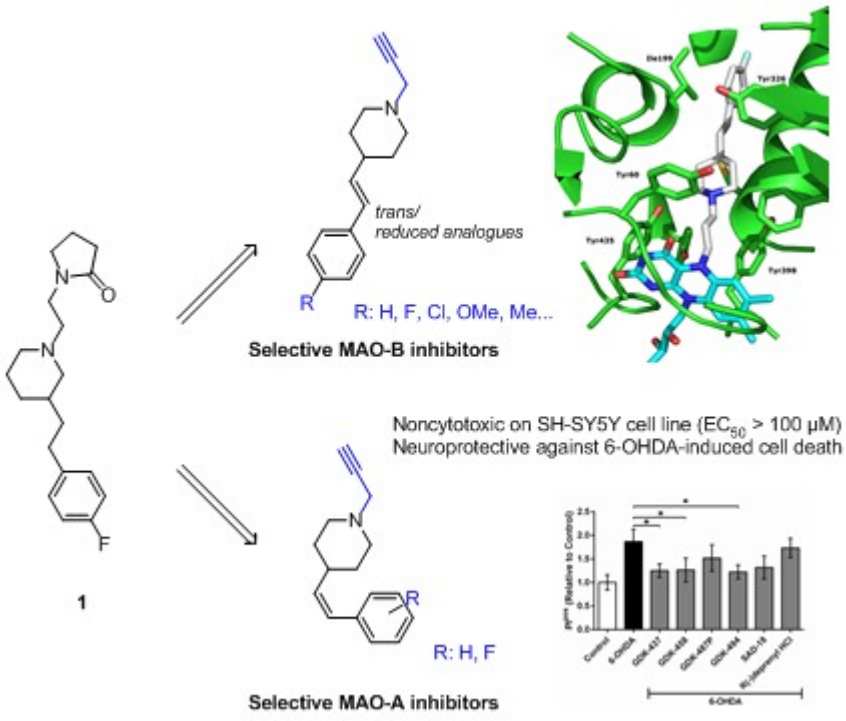

Figure 1: Development of N-propargylpiperidines as selective MAO-A/MAO-B inhibitors.

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DESIGN OF NOVEL GPCR FAMILY-TARGETED SCAFFOLDS: SYNTHETIC AND CHEMINFORMATIC EXPLORATION OF NOVEL MEDICINAL CHEMISTRY SPACE

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Matching the synthetically accessible chemical space with disease-related biological target space is one of the core activities of current medicinal chemistry. The content of today's compound collections is a reflection of the target families that have been addressed in the past, and chemical libraries are a reflection of the number and type of chemical reactions we can pursue in e.g. a 2 week chemistry/biology cycle time typically embedded in lead finding campaigns. Hence, there remains a substantial risk that currently populated compound space might not match with the areas of biological target space the pharmaceutical industry will have to focus on in the near future. However, chemical complexity, associated with synthetic challenges prevented medicinal chemists from a systematic exploration of e.g. natural product-related compound space over the last two decades, despite the obvious structural complementarity of natural product-derived analogues to main stream libraries.

Within our design and synthesis work we embark into a systematic exploration of fused, bridged, and spiro-cyclic systems in which a smaller ring (3 to 7 skeleton atoms) is associated with a medium-sized ring (7 to 12 skeleton atoms, figure 1). We will elaborate on the results of a systematic cheminformatics and data mining analysis of the charted bioactive compound space, followed by structure-based designs of novel, thus patentable bicyclic ring topologies. Subsequent synthetic feasibility considerations are then fueling chemical validation of new bicyclic ring systems that qualify as scaffolds for 2D and 3D library expansion.

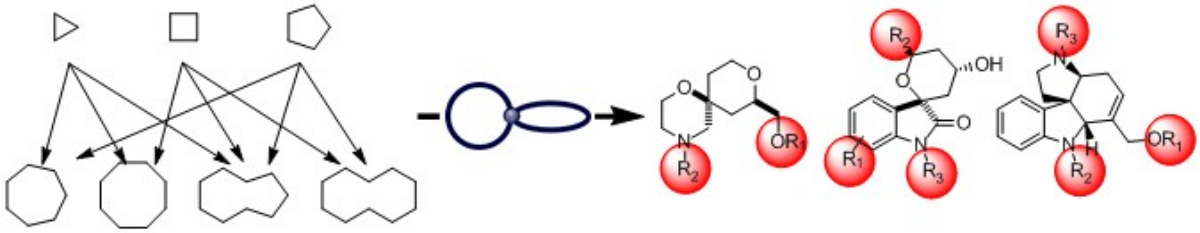

Figure 1: Schematic illustration of the design principles for spiro fused bicyclic topologies

In pursuit of this concept, we try to achieve an optimal balance between novelty on one hand, and proximity to bioactive compound space, i.e. resemblance of peptide secondary structure elements, and increased 3D skeletal complexity on the other hand. We consider this as a significant contribution to unlock the chemical accessible bicyclic ring system space that is often inaccessible in lead finding and lead optimization campaigns due to the underlying chemical complexity.

PRIVILEGED STRUCTURES: A VERSATILE CONCEPT TO EXPLORE NEW CHEMICAL SPACE WITH MEDICINAL CHEMISTRY UTILITY

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Today's most prominent therapeutically relevant targets cluster into densely populated gene families which exhibit structural and functional commonalities in terms of molecular recognition. Thorough analysis of these shared features allows for the definition of key pharmacophoric elements that can be imprinted into novel scaffolds from which small-molecule modulators of those target proteins can emerge.

We have focused our interest on the multi-member target class of the G protein-coupled receptors and analyzed the relevant family-wide recognition elements that can be exploited for small-molecule design. Heterocycles are major constituents of drug candidates, thus there is constant need for novel heterocyclic systems that either qualify as novel core structures for lead finding and optimization campaigns, or contribute to target binding by specific heterocycle-encoded interaction partners in the context of bio-isosteric replacement strategies.

This talk will give a qualitative and quantitative assessment of the heterocycle chemical space with high medicinal chemistry utility. Topological attributes required exploring useful but unused chemical space will be discussed, emphasizing the level of condensation and saturation within heterocyclic systems.

The concept of target family-directed privileged structures will be highlighted. Novel chemotypes will be introduced that have pre-engineered structural and functional privileges in that they address target family-wide commonalities in terms of ligand recognition and conformational transitions. Such privileged structures can be used e.g. as scaffolds for subsequent library design and enumeration and have the potential to provide useful hit structures as starting points for compound optimization programs.

5-((-)-BORNYLOXY)-3,4-DICHLORO-2(5H)-FURANONE SPECIFICALLY TARGETS A BIOFILM-EMBEDDED FOODBORNE HUMAN PATHOGEN BACILLUS CEREUS

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Bacterial infections caused by multi-drug resistant bacteria are a great challenge in medicine and prompt the requirement for the novel antimicrobial agents. *B. cereus* is an underestimated emerging pathogen causing wound infections, bacteraemia, septicaemia and pneumonia in among immunocompromised patients and can be involved in fatal healthcare-associated infections in premature newborns. Similarly to many other bacteria, *B. cereus* forms rigid biofilms on tissues and artificial surfaces drastically reducing thereby bacterial susceptibility to antibiotics. Therefore, conventional treatment and disinfection regimens may be inefficient and to the dissemination of resistance.

The combination of antibiotics with biofilm-modifying agents seems as a promising strategy. Here we report that derivatives of 3,4-dihalo-2(5*H*)-furanone possessing either *l*-menthol or *l*-borneol moieties efficiently inhibit the growth and the biofilm formation by *B. cereus* and increases aminoglycosides efficiency against this bacteria. Among four compounds tested 5-((-)-bornyloxy)-3,4-dichloro-2(5*H*)-furanone designed as F123 was the most active with MIC of 8 mg/ml for *S. aureus, S. epidermidis, M. luteus* and *B. cereus* and 16 mg/ml for *B. subtilis*. F123 also completely prevented the biofilm formation by these bacteria at concentration of MIC. The Gram-negative bacteria such as *E. coli*, *S. typhimurium, E. aerogenes, K. pneumonie* and *P. aeruginosa* were not susceptible to the compound. Interestingly, the minimum bactericidal concentration (MBC) was detected only for *B. cereus* bacteria and was equal to its MIC value (8 mg/ml). For other strains it exceeded 128 mg/ml. We analyzed the time-kill curves for F123 against Gram-positive *S. aureus, S. epidermidis, M. luteus*, *B. subtilis*, *B. cereus* and one Gram-negative bacteria *E. coli* as a control. F123 exhibited bacteriostatic features at concentration of 4×MIC against *S. aureus, S. epidermidis, M. luteus* and *B. subtilis.* By contrast, F123 demonstrated selective bactericidal action on *B. cereus* by killing all bacteria within 8 h at 4×MIC. Other compounds where chlorine was replaced by bromine and / or *l*-menthol exhibited much lower activities. Nevertheless, all compounds exhibited synergy with gentamycin and amikacin when tested against *B. cereus*, with FICI values of 0.25-0.45, and reduced twice the MICs of antimicrobials at 0.5-1 mg/ml. Moreover, F123 was also capable to kill *B. cereus* biofilm-embedded cells. Similar effect was observed for the relative bacteria *B. subtilis,* although not so pronounced, suggesting the selectivity of F123 to *Bacillus*.

Taken together our data shows that derivatives of 2(5*H*)-furanone possessing either *l*-menthol or *l*-borneol moieties could be interesting start point for developing of new approach for *B. cereus* infections.

This work was supported by the Russian Science Foundation, grant No 15-14-00046

DISCOVERY OF THE CLINICAL CANDIDATE AZD1390: A HIGH QUALITY POTENT AND SELECTIVE INHIBITOR OF ATM KINASE WITH THE ABILITY TO CROSS THE BLOOD BRAIN BARRIER

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Glioblastoma multiforme (GBM) is the most common and lethal form of primary brain tumor and current treatment (surgery followed by fractionated radiotherapy and temozolomide) provides a median survival of just 12-15 months.[1] The poor prognosis associated with GBM is attributed to an extensive infiltration into surrounding brain tissue (thereby limiting the effectiveness of surgical excision), an intrinsic chemo/radioresistance of the tumor and the presence of the blood-brain barrier (BBB) which limits the ability of certain chemotherapies to reach the tumor. Ataxia telangiectasia mutant (ATM) is a serine/threonine protein kinase from the phosphatidylinositol 3-kinase-related kinase (PIKK) family of protein kinases and plays a crucial role in the cellular DNA damage response signalling activated by DNA double strand breaks (DSB). Activated ATM promotes DNA repair and S/G1-cell cycle checkpoints to prevent premature mitosis, maintain genomic integrity and promote appropriate cell survival or death pathways. DSBs arise intrinsically through the collapse of stalled replication forks, which are induced by a wide range of chemotherapies, or extrinsically through exposure to ionising radiation. Therefore, ATM inhibition represents an exciting clinical opportunity as a target to hyper-sensitize tumors to chemo/radiotherapy.

The optimization of compound properties suitable to allow efficient BBB penetration remains a significant challenge within Medicinal Chemistry and failure to consider these can severely restrict the utility of an agent for CNS disease. Herein, we describe the identification of AZD1390, a first in class orally available and CNS penetrant ATM inhibitor suitable for the treatment of intracranial malignancies. This presentation represents the first oral disclosure of the Medicinal Chemistry strategies employed to optimize BBB-penetration, alongside the SAR for ATM potency, selectivity and pharmacokinetic properties. AZD1390 is an exceptionally potent inhibitor of ATM in cells (IC_{50} = 0.78 nM) with >10,000 fold selectivity over closely related members of the PIKK family of enzymes and excellent selectivity across a broad panel of kinases. AZD1390 displays excellent oral bioavailability in preclinical species (66% in rat and 74% in dog), is not a substrate for human efflux transporters and has been shown to efficiently cross the BBB in Non-Human Primate PET studies. Profound tumor regressions and increased animal survival (>50 days) have been observed in orthotopic xenograft models of brain cancer following just 2 or 4 days combination treatment of AZD1390 with radiotherapy, compared to radiotherapy treatment alone. These data support the potential of CNS penetrant ATM inhibitors to provide an important new therapeutic agent for the treatment of intracranial malignancies. AZD1390 is currently undergoing early clinical assessment.

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NEW CANCER THERAPEUTIC MODALITIES EMPLOYING CYCLOPROPYLINDOLE AND SECO-CB!-INDOLE ANALOGS AND PRODRUGS. EXTENSIVE PRECLINICAL STUDIES IN CANCER CELL LINES AND HUMAN TUMOR XENOGRAFT MODELS SYSTEMS DEMONSTRATE HIGHLY POTENT AND SPECIFIC ANTI-CANCER ACTIVITY

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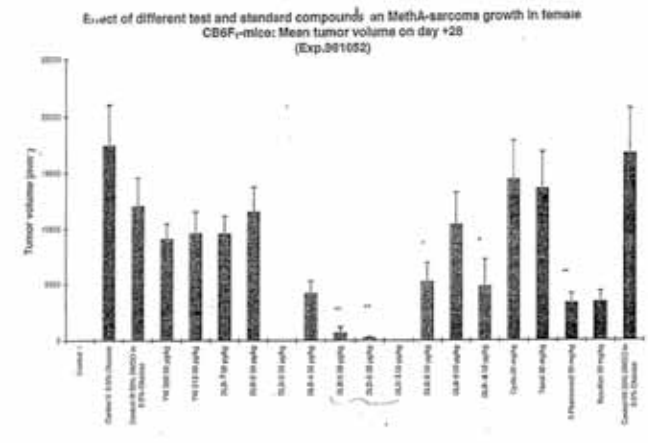
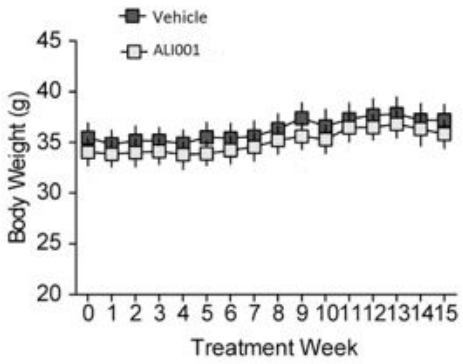
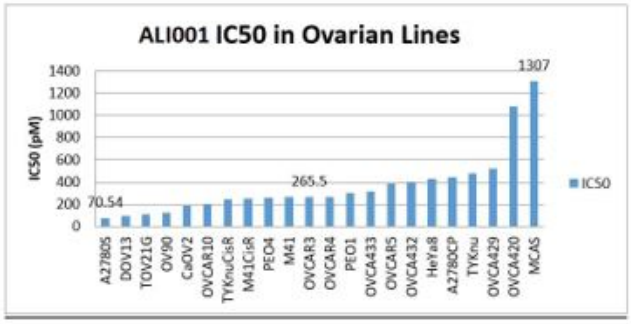
A series of highly potent analogs related to Seco-CBI-(Indole)2 with varying subsituents around the core DNA alkylating subunit have been synthesized and analyzed for their antitumor activity in a series of human tumor cell lines both 'in-vitro' and 'in-vivo' in a series of murine human tumor xenografts. Out of 23 synthetic compounds screened 3 were selected for further studies both in platinum resistant ovarian cancer cell lines and several human lung cancer cell lines. Toxicity studies of the 3 lead NCE's was performed and minimal 'in vivo' toxicity was observed. These compounds show promise as novel anti-cancer therapeutic agents either as single agents, prodrugs or in combination therapies.







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ANTIMICROBIAL EFFECTS OF SULFONYL DERIVATIVE OF 2(5H)-FURANONE AGAINST BIOFILM ASSOCIATED STAPHYLOCOCCUS AUREUS

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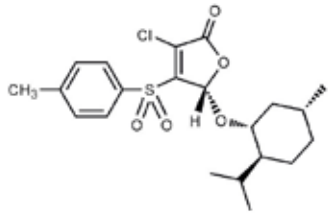
The biofilm formation by the methicillin-resistant *Staphylococcus aureus* (MRSA) cells on wounds and surfaces contacting with different tissues makes bacteria inaccessible to antimicrobials and immune system of the body. The discovery of the natural furanones derivatives with a biofilm suppression activity gave the rise of investigations of these compounds as antibiofilm agents. While many 2(5*H*)-furanone derivatives interfere with AI-II quorum-sensing systems of Gram-negative bacteria blocking thereby the biofilm growth, a number of furanones were shown to repress the biofilm formation by *Bacillus subtilis* and *Staphylococci.* Here we show that the novel 2(5*H*)-furanone derivative possessing sulfonyl group and *l*-menthol moiety (**F105**) exhibits synergy with aminoglycosides against the *S. aureus* and demonstrates attractive activity towards the biofilm-embedded bacteria.



Structure of the furanone F105

The 2(5*H*)-furanone derivative **F105** was synthesized in three steps from commercially available mucochloric acid. The minimal inhibitory concentration (MIC) was two-fold higher (20 mg/L) in the MRSA compared to the methicillin-sensitive strain (MSSA) and it can be assumed that 10-20 mg/L (corresponding to 25-50 μM) **F105** might be the effective MIC-range in staphylococci. The minimal bactericidal concentration (MBC) value of **F105** was found to be 40 mg/L in MSSA and 160 mg/L in MRSA. The time-kill curves revealed that all cells of MSSA exposed to **F105** at concentration of 2×MBC were killed within eight hours of treatment. Alternatively, 1×MBC of **F105** led to the reduction in the number of viable cells by three orders of magnitude within 12 hours. Synergism of **F105** was observed when combined with aminoglycosides: the fractional inhibitory concentration index (FICI) values for **F105** were determined to be 0.33±0.04 in combination with amikacin, 0.33±0.16 with gentamicin and 0.44±0.17 with kanamycin. Besides aminoglicosides, strong synergy has been observed also for benzalkonium chloride with FICI of 0.29 ± 0.09. The CLSM analysis indicated that treatment with **F105** did not lead to any visibly remarkable decrease of the biofilm thickness, while the ratio of dead/viable cell increased significantly in the concentration dependent manner. the antimicrobial activity of **F105** is moderate, but its effect in established biofilms was surprisingly strong and exceeded the activity of conventional antibiotics by several magnitudes.

The mechanism of action of **F105** remains so far elusive. The preliminary screening of the potential molecular targets of the **F105** has shown that the intracellular level of many proteins in *S. aureus* decreases when growing at 0.5xMIC of **F105**, the most of them are enzymes involved in main cellular metabolism. These data suggest that apparently **F105** targets rather some common cellular processes than quorum sensing-depending processes. Taking in account that already 0.5-0.7 mg/L of **F105** decreases the MICs of aminoglycosides and benzalkonium chloride twofold, and the ability of **F105** to target the biofilm-embedded *Staphylococci*, its chemotype looks as attractive tool for combination with antimicrobials to reduce their therapeutic concentrations, as well as to decrease their side effects and to enhance the efficacy of treatment of both planctonic and biofilm-embedded bacteria.

This work was supported by the Russian Science Foundation, grant No 15-14-00046

ALBUBINDERS: SMALL MOLECULE HSA BINDERS FOR HALF-LIFE EXTENSION OF THERAPEUTICS

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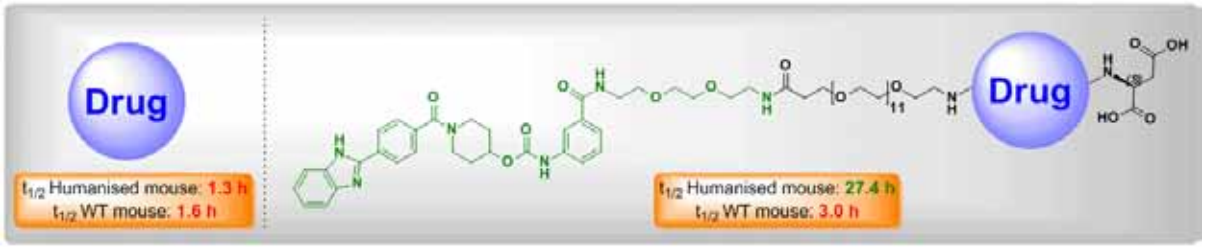
Non-adherence to chronic medicines averages 50%, leads to increased morbidity/mortality and is estimated to cost healthcare systems around $100 billion a year.[1] Therefore, it is important to reduce clearance of highly potent drugs, thus extending their pharmacology *in vivo*. However, current approaches to half-life extension such as PEGylation, lipidation and other bioconjugation techniques can be expensive and/or present challenges in development.[2] Here we investigate the potential of extending the half-life of drugs through binding to Human Serum Albumin (HSA) using high-affinity, non-covalent small molecule Albubinders. The aim of this project is to develop a soluble and stable platform for half-life extension of therapeutics.

This project involves generation and screening of compounds using DNA encoded libraries, small molecule and conjugate synthesis, computational modelling, and a variety of biophysical, biological, *in vitro* and *in vivo* studies. In the end, human specific AlbuBinder chemotypes were discovered and conjugated to a cargo, extending its *in vivo*half-life from 1 hour to more than 24 hours in humanised mice. Good solubility and potency were maintained.



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DEVELOPMENT OF INHIBITORS OF MSBA: FROM HTS TO GRAM-NEGATIVE WILD-TYPE ACTIVITY

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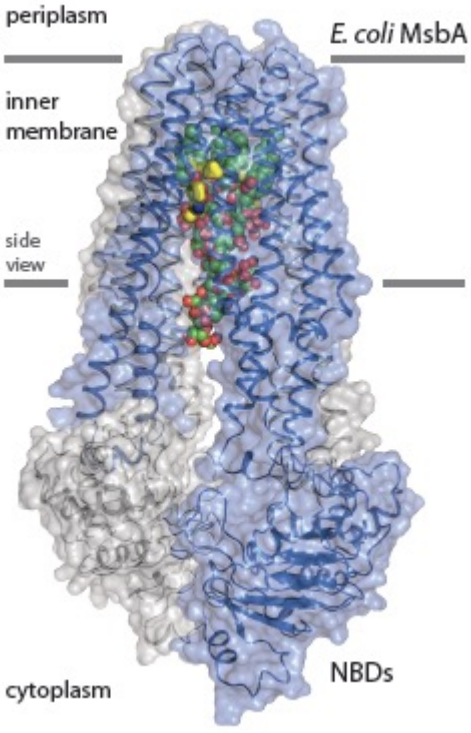
The dramatic increase in the prevalence of highly multi-drug resistant Gram-negative infections and the corresponding lack of new classes of antibiotics is projected to result in approximately 10 million deaths per year by 2050 according to the World Health Organization. There is a critical need for the discovery of anti-infectives with new modes of action which would help alleviate the high levels of resistance to the known classes of antibiotics commonly present in bacteria today. We report on our program to target the Gram-negative ATP-binding cassette (ABC) transporter MsbA, an essential inner membrane protein that transports core lipopolysaccharide (LPS) from the cytoplasm to the periplasmic face of the inner membrane. We demonstrate the improvement on a hit from a high throughput screening (HTS) assay into compounds with single digit micromolar (μM) minimum inhibitory concentrations (MICs) against wild-type *E.coli*. This was accomplished despite the lack of compounds with traditional gram-negative antibiotic physicochemical properties contained in typical HTS sets. A high-resolution 2.9 Å crystal structure of MsbA with an inhibitor bound was obtained during the course of this medicinal chemistry optimization, revealing a new mode of action for inhibition of an ABC transporter.



A MODULAR SYNTHESIS OF TETRACYCLIC MEROTERPENOID ANTIBIOTICS

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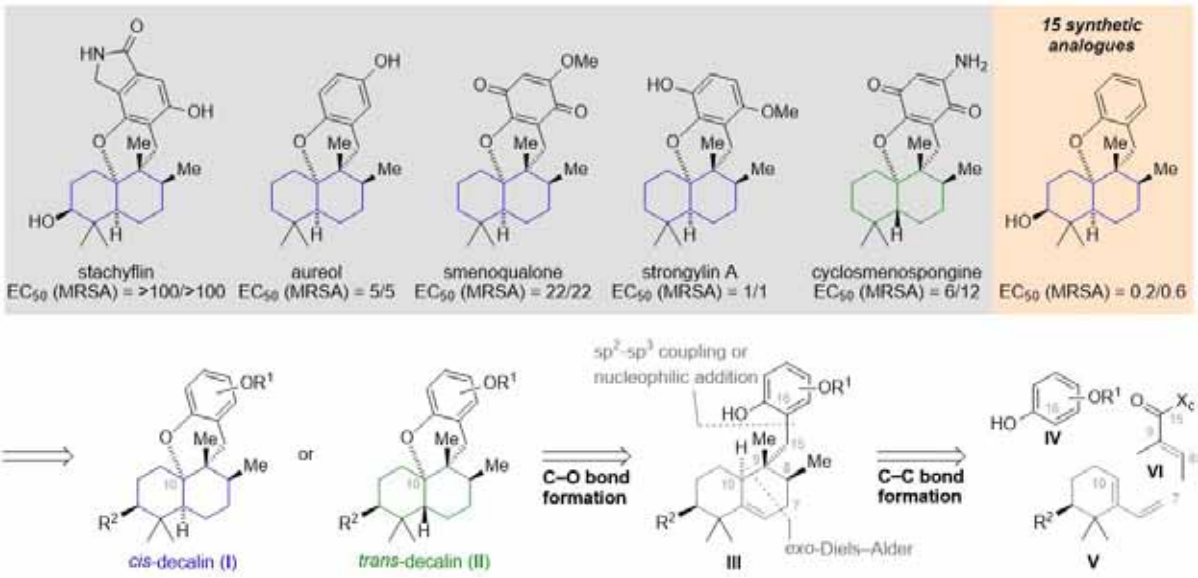
Stachyflin, aureol, smenoqualone, strongylin A, and cyclosmenospongine belong to a family of tetracyclic meroterpenoids, which, by nature of their unique molecular structures and various biological properties, have attracted synthetic and medicinal chemists alike.[1–7] Despite their obvious biosynthetic relationship, only scattered reports on the synthesis and biological investigation of individual meroterpenoids have appeared so far.[1,2,4–12] Herein we report a highly modular synthetic strategy that enabled the synthesis of each of these natural products and 15 non-natural derivatives. The route employs an auxiliary-controlled Diels–Alder reaction to enable the enantioselective construction of the decalin subunit, which was connected to variously substituted arenes by either carbonyl addition chemistry or sterically demanding sp^2–sp^3 cross-coupling reactions. The selective installation of either the *cis*- or *trans*-decalin stereochemistry was accomplished by an acid mediated cyclization/isomerization reaction. Structural variation of the arene and decalin component enabled rapid extension of the natural products library and provided access to several non-natural analogues that were previously inaccessible via semi-synthesis. Biological profiling of the formerly inaccessible compound library revealed that strongylin A and a simplified derivative thereof have potent antibiotic activity against methicillin-resistant *Staphylococcus aureus*. The effective concentrations (EC_{50} values) that inhibited the growth of two MRSA strains (DSM 11822/RKI 11-02670) are given in μM.



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DISCOVERY OF SMALL MOLECULE PCSK9 INHIBITORS

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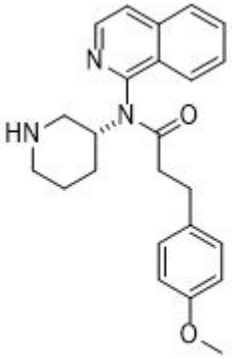
The optimization of a new class of small molecule PCSK9 translation inhibitors is described. The potency, physicochemical properties and the off-target pharmacology associated with the hit compound PF-00932239 were improved by changes to two regions of the molecule. The last step in the construction of the congested amide center was enabled by three different routes. Subtle structural changes yielded significant changes in pharmacology. These efforts culminated in the identification of PF-06446846 with rat pharmacokinetics suitable for in vivo evaluation. In a two-week rat safety and efficacy study PF-06446846 showed both PCSK9 and cholesterol lowering but a narrow therapeutic margin. Further optimization led to molecules with improved therapeutic margins.



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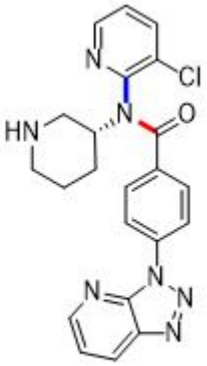

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POSTERS

Late Stage Functionalization

SYNTHESIS OF LEUCOSCEPTROID NATURAL PRODUCT DERIVATIVES FOR TARGET IDENTIFICATION

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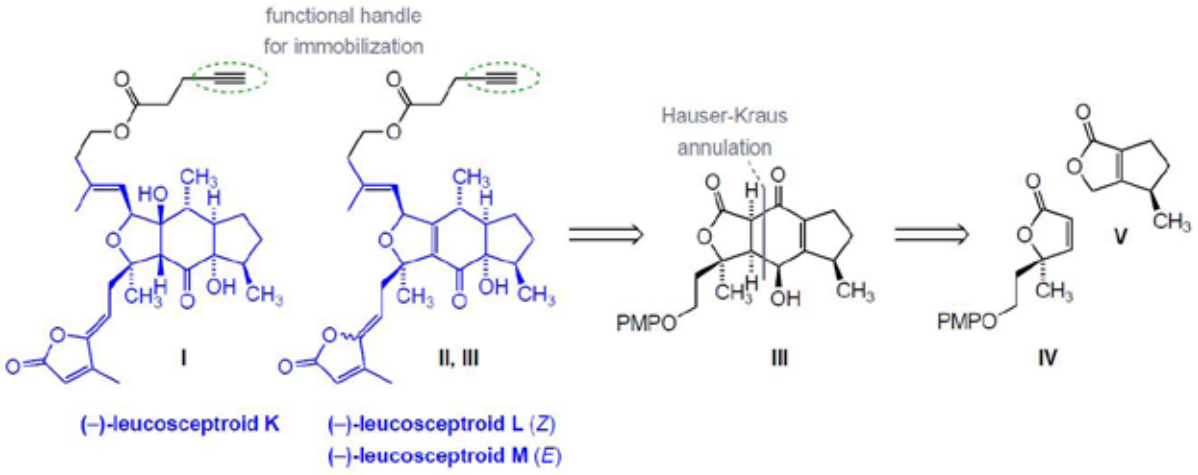
The leucosceptroid natural products were isolated from *Leucosceptrum canum* Smith, a native plant in Nepal and China, by Li and coworkers.[1–6] These sesterterpenoids display nanomolar antifeedant activity against both the cotton bollworm and the beet armyworm, some of the most destructive agricultural pests in nature.

The recent total synthesis of sixteen members of the leucosceptroid family of natural products by our laboratory provided enough material for further investigations of the biological activity of these terpenoids.[7–9] In addition to the significant antifeedant activity, the group of Adibekian (University of Geneva, Scripps Research Institute - Florida) found that some leucosceptroid natural products interact highly selectively with proteins that are involved in the development of cancer.[10] In this respect, leucosceptroids K, L and M revealed the most favourable effects. It is hypothesized, that the remarkable structure-activity relationship of these natural products arises from the butenolide moiety, which they have in common. Suitably modified leucosceptroids for target identification via affinity proteomics could help to understand the mode of action with which small molecules can influence cancer development.

Herein, we describe the synthesis of three derivatives **I**, **II** and **III**, which correspond to leucosceptroids K, L and M. The synthesis intercepts our general entry to the leucosceptroids and is based on a late stage intermediate of the synthetic route.



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