Emerging therapies for acute myeloid leukaemia using hDHODH inhibitors able to restore in vitro and in vivo myeloid differentiation

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VIII EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry

Athens, Greece | September 1 - 5, 2019

SYMPOSIUM CHAIRS

- **Varinder AGGARWAL** (UNIVERSITY OF BRISTOL, United Kingdom)
- **Spiros LIRAS** (BIOGEN, United States)

Book of Abstracts

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TABLE OF CONTENT

NOTES

Opening Lecture – Biography & Abstract

PROF. K. C. NICOLAOU

RICE UNIVERSITY, Houston, United States

K. C. Nicolaou is currently the Harry C. Olga K. Wiess Professor of Chemistry at Rice University. He previously served concurrently as the founding chairman of the Chemistry Department at the Scripps Research Institute, a distinguished Professor of Chemistry at the University of California, San Diego (1989-2013), and the founding Director of the Chemical Synthesis Laboratory at ICES, A*STAR at Biopolis, Singapore.

His research activities focus on the discovery and development of new synthetic strategies and technologies, and their applications to the total synthesis of natural and designed molecules of biological and medical importance. He is a co-author of the *Classics in Total Synthesis series (I, II, III) and Molecules that Changed the World.*

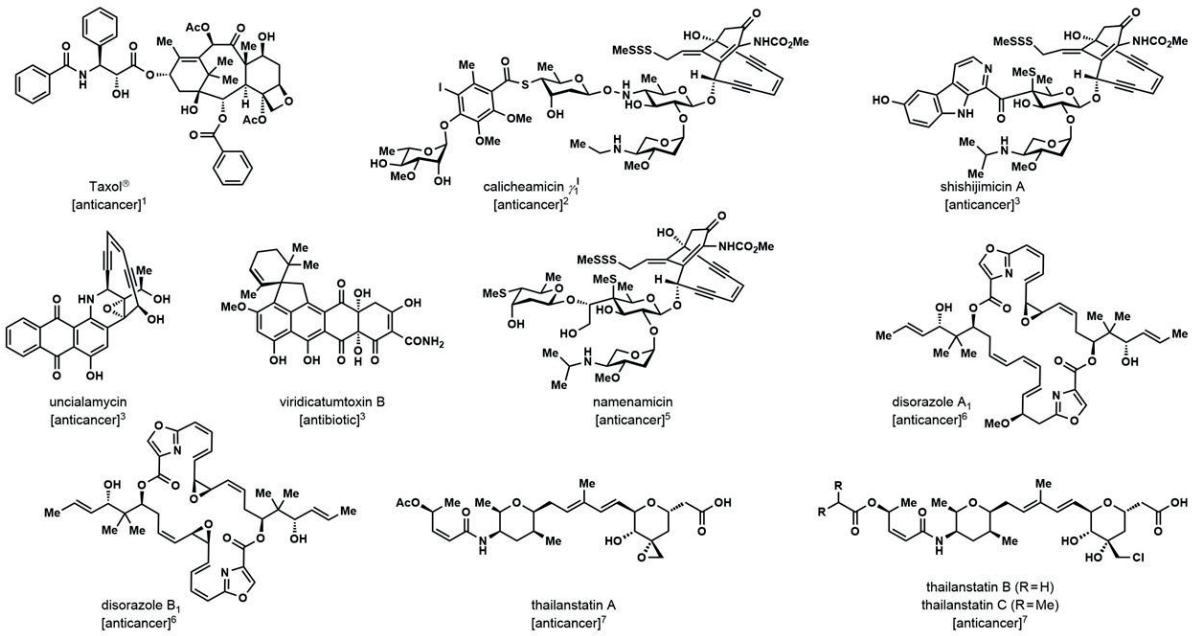
T01

THE ART AND SCIENCE OF TOTAL SYNTHESIS AND ITS IMPACT ON BIOLOGY AND MEDICINE: FROM THE FUNDAMENTALS TO THE TRANSLATIONAL

K. C. Nicolaou

Harry C. and Olga K. Wiess Professor of Chemistry
Department of Chemistry, Rice University, Houston, TX 77005, USA

In this lecture, a brief historical overview of organic synthesis and its impact on biology and medicine will be followed by highlights of advances in total synthesis from the speaker's laboratories. Specifically, the total synthesis of natural and designed molecules of biological and medical importance will be presented, including the anticancer agents Taxol®, calicheamicin γ_1^I, shishijimicin A, uncialamycin, and antibiotic viridicatumtoxin B, namenamicin, disorazoles A1 and B1, and thailanstatins A, B and C. The lecture will also touch upon the impact of total synthesis on the advent of antibody drug conjugates (ADCs) for targeted cancer therapies.



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NOTES

Invited Lectures – Biographies & Abstracts

PROF. MARGARET ANNE BRIMBLE

THE UNIVERSITY OF AUCKLAND, Auckland, New Zealand

Margaret Brimble is the Director of Medicinal Chemistry and a Distinguished Professor at the University of Auckland, New Zealand where her research program focuses on the synthesis of bioactive natural products, antimicrobial peptides, cancer vaccines, glycopeptides, self-assembling peptides and peptidomimetics. She has published >460 papers, 60 reviews and is an inventor on >30 patents.

In 2018 she was elected a Fellow of the Royal Society London and was awarded the Royal Society of Chemistry George and Christine Sosnovsky Award in Cancer Therapy. She won the 2016 Marsden Medal, the 2012 RSNZ Rutherford (NZ's top science prize), MacDiarmid and Hector Medals, the 2011 Royal Australian Chemical Institute Adrien Albert Award, the 2010 RSC Natural Products Award, the 2007 L'Oreal-UNESCO Women in Science laureate in Materials Science for Asia-Pacific, a 2015 IUPAC Distinguished Women in Chemistry/Chemical Engineering Award and conferred the Queen's Honour CNZM. She is Past-President of IUPAC Organic and Biomolecular Division III, an Associate Editor for Organic and Biomolecular Chemistry, Past-President of the International Society of Heterocyclic Chemistry and Past-Chair of the Rutherford Foundation RSNZ. She discovered the first drug named "trofinetide" to treat Rett Syndrome and Fragile X syndrome that is in phase III clinical trials with Neuren Pharmaceuticals. Trofinetide is New Zealand's first successful drug and one of only a few to be discovered in an academic laboratory. Margaret also co-Founded the spin-out company SapVax with US$6 million funding from BioMotiv USA to take self-adjuvanting cancer vaccines based on a novel chemistry platform, to clinical trial (see: https://sapvaxllc.com).

T02

NATURE'S MEDICINE CHEST: OPPORTUNITIES FOR SYNTHESIS AND DRUG DISCOVERY

Margaret Anne Brimble

The University of Auckland, Science Centre - Chemistry, 23 Symonds St, 1010 Auckland, New Zealand

The synthesis of several bioactive natural products as “privileged scaffolds” for drug discovery will be described. This lecture will also showcase research on the synthesis of peptides, lipopeptides and glycopeptides as a platform for the discovery and development of peptide therapeutics as agents to treat neurogenetic disorders, infectious disease, cancer and diabetes. One example includes the peptidomimetic drug candidate trofinetide (NNZ2566) that has been granted orphan drug status and fast track designation by the US FDA and is currently being evaluated in a final phase III clinical trial undertaken by Neuren Pharmaceuticals (see: http://www.neurenpharma.com/IRM/content/default.aspx) to treat Rett Syndrome. The synthetic chemistry that resulted in the founding of the “spin-out” company SapVax with US$5.5 million investment from BioMotiv in Cleveland, Ohio to develop a suite of “first-in-class cancer vaccines” based on a novel self-adjuvanting peptide chemistry platform for immuno-oncology applications (see:https://sapvaxllc.com) will also be described.

PROF. OLIVER PLETTENBURG

LEIBNIZ UNIVERSITY HANNOVER, Hannover, Germany

Oliver Plettenburg, PhD, is full professor for 'Medicinal Chemistry' at Leibniz Universität Hannover and director of the Institute of Medicinal Chemistry of the Helmholtz Center Munich. Before rejoining academia he spent more than fourteen years in a major pharmaceutical venture, last he held positions as "Head of Chemical Biology" and "Head of Biosensors and Chemical Probes".

His research focuses on hit and lead optimization of promising compounds for treatment of devastating diseases, development of innovative targeted and smart drug delivery methods and synthesis of novel imaging agents for in-vivo monitoring of pathogenesis.

T03

DRUG DISCOVERY IN ACADEMIA

Oliver Plettenburg

Leibniz University Hannover, Institute of Medicinal Chemistry, Schneiderberg 1 B, 30167 Hannover, Germany

Despite all efforts and scientific advances, success rates in current drug development are still unsustainably low. Some of the challenges of drug discovery and potential contributions of academia will be discussed.

As an example, an improved understanding of the animal models used for selecting compounds for further progression can be regarded as a key for successful drug development and needs to be addressed already at early project stages. Particularly animal models resembling chronic diseases are frequently compromised by high inter-animal variability and heterogeneous disease development, resulting in the necessity to employ large groups of animals to reach statistical significance.

A major challenge in the development of novel therapeutics for these diseases is thus to properly characterize the disease state of an individual animal at a given point in time in an ongoing longitudinal pharmacological study to define the most appropriate timepoint for therapeutic intervention and to properly assess the efficacy of the applied drug in vivo.

Different aspects and applications of molecular imaging based approaches to facilitate preclinical drug development will be presented. This will particularly include illustrating examples for in-vivo imaging of enzymatic activity and design and characterization of targeted imaging reagents to improve characterization of distinct disease stages. Consequent implementation of similar target validation approaches will lead to an improved understanding of disease pathogenesis and of the employed animal models and thus ultimately reduce attrition rates.

DR MICHAEL MICHAELIDES

ABBVIE, North Chicago, United States

Michael earned his B.Sc. degree in chemistry from Stony Brook University and his doctorate in organic chemistry from the Massachusetts Institute of Technology. He joined Abbott immediately after completing his graduate studies.

During his 30-year tenure at Abbott and now Abbvie, Michael has carried out research in the areas of Neuroscience, Immunoscience and Oncology. He has contributed to the invention and advancement of several clinical candidates, including adrogolide for the treatment of Parkinson's disease and linifanib for hepatocellular carcinoma. He has over 40 issued patents and over 50 published articles to his name.

Michael is currently Senior Research Fellow, Senior Director of Oncology Chemistry and a member of the Global Abbvie Medicinal Chemistry Leadership Team.

T04

DISCOVERY OF FIRST IN CLASS, ORALLY BIOAVAILABLE P300/CBP HAT DOMAIN INHIBITORS

Michael Michaelides

AbbVie Inc., 1 North Waukegan Rd., North Chicago, IL 60064, United States

Reversible protein acetylation has emerged as a key signaling mechanism for regulating cellular function and, in particular, transcription regulation. Acetylation of protein lysine residues is mediated by a family of histone acetyltransferases (HATs) whereas removal of acetyl groups is catalyzed by histone deacetylases (HDACs). Small molecule HDAC inhibitors have been successfully developed as novel therapeutic agents for the treatment of certain cancers, however progress on HAT inhibitors has been limited due to the lack of selective, drug like inhibitors. Two of the best described HAT's are p300 and the closely related paralog CBP. p300/CBP acetylates histones as well as numerous transcription factors to facilitate gene activation programs important for cell growth and differentiation. Inhibition of p300/CBP has been proposed as a therapeutic strategy in diseases driven by gene activation such as cancer, Alzheimer's disease, diabetes and cardiovascular diseases.

Due to the multiple biologically relevant domains of p300 as well as its scaffolding functions, genetic knockdown approaches cannot be used to study the consequences of HAT domain inhibition alone. Thus, selective small molecule inhibitor compounds are needed to understand the therapeutic potential of p300 HAT inhibition. Widely used literature compounds suffer for either poor cell permeability or poor pharmacologic specificity. We have developed a series of novel, highly selective and orally bioavailable histone acetyltransferase (HAT) domain inhibitors p300/CBP inhibitor that are suitable for in vitro and in vivo target validation studies. The medicinal chemistry campaign starting from a unique hydantoin screening hit identified through virtual ligand screening and the subsequent optimization to improve cell potency and pharmacokinetic properties will be described. During the prosecution of this project a high resolution co-crystal structure of a small molecule inhibitor (A-485) bound to the catalytic active site of p300 HAT was obtained. The use of this structure to further drive optimization and the structure based design of covalent inhibitors will also be discussed.

DR CORNELIA ZUMBRUNN

IDORSIA PHARMACEUTICALS, Allschwil, Switzerland

Cornelia Zumbrunn holds a position as Principal Scientist (medicinal chemist and project leader) in the field of antibacterial research and cardiovascular diseases. Since 2004 she worked in the research department of Actelion Pharmaceuticals Ltd, now Idorsia Pharmaceuticals Ltd. (Allschwil, Switzerland). Previous positions include Morphochem AG and Hoffmann-LaRoche, after a postdoc at Cambridge University (UK).

Cornelia obtained her PhD from Hoffmann-LaRoche and the University of Zürich after having completed studies in organic chemistry in Fribourg (CH) and Neuchâtel (CH).

Her research focused on the discovery of antibiotics with novel modes of action and other projects in the areas of central nervous systems and cardiovascular research.

She is a board member and the secretary of the Division of Medicinal Chemistry and Chemical Biology of the Swiss Chemical Society (DMCCB).

T05

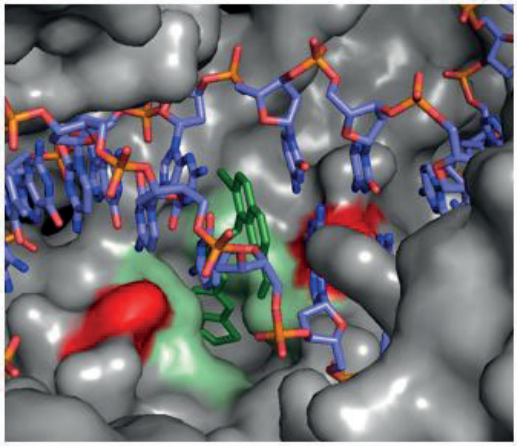
NOVEL BACTERIAL TOPOISOMERASE INHIBITORS (NBTI) WITH POTENT GRAM-NEGATIVE ACTIVITY

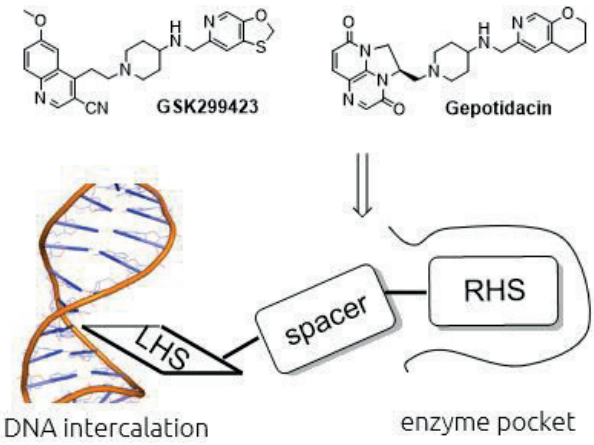
Cornelia Zumbrunn (1), Daniel Ritz (1), Thierry Bruyere (1), Hans H. Locher (2), Georg Rueedi (1)

1) Idorsia Pharmaceuticals Ltd., Hegenheimermattweg 91, CH-4123 Allschwil, Switzerland
2) current address: Polyphor Ltd., Hegenheimermattweg 125, CH-4123 Allschwil, Switzerland

The need for novel antibiotics against the most difficult to treat pathogens (**E**nterococci, ***S****taphylococcus aureus*, ***K****lebsiella pneumoniae*, ***A****cinetobacter baumannii,* ***P****seudomonas aeruginosa*, and ***E****. coli)*, the so-called ESKAPE pathogens is undisputed. Novel agents should be devoid of cross-resistance with antibiotics currently used in the clinic.

The novel bacterial topoisomerase inhibitors (NBTI) such as GSK 299432 or gepotidacin are an attractive class of compounds acting via a different mode of action as compared to fluoroquinolones or compounds binding at the ATP binding site such as novobiocin. NBTIs stabilize a ternary complex between the enzyme (A_2B_2 complex in gyrase), DNA and inhibitor. While the right hand side of the molecule (RHS) is anchored in a pocket formed by the two A subunits of Gyrase (coloured in light green), the left hand side (LHS) is intercalated into the complexed strand of DNA.[1,2]





We report here the discovery of dual inhibitors of gyrase and topoisomerase IV, with coverage of all ESKAPE pathogens, improved penetration and decreased efflux liabilities in Gram-negative species.

During our investigations we discovered a wide range of structural modifications that were tolerated and which led to compounds with varying antibacterial spectrum. Activity on Gram-negative species was mainly driven by improved intracellular accumulation of the inhibitors, i.e. improved penetration and decreased efflux but also by increased potency.

We disclose here findings and learnings of our investigations on a journey through the chemical space of the Actelion/Idorsia which led to the discovery of several classes of compounds highly potent on ESKAPE pathogens.

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PROF. JOHN BOWER

UNIVERSITY OF BRISTOL, Bristol, United Kingdom

John F. Bower obtained his MSci degree in 2003 from the University of Bristol, where he remained to study for his PhD degree (2007) under the guidance of Professor Timothy Gallagher. He then undertook postdoctoral appointments with Professor Michael Krische at the University of Texas at Austin (2007-2008) and Professor Timothy Donohoe at the University of Oxford (2008-2010). In 2010, he was awarded a Royal Society University Research Fellowship and commenced his independent career at the University of Bristol.

The group's research interests lie broadly within the area of synthetic chemistry, with a focus on N-heterocyclic methodologies and metal-catalysed processes. Bower's research has been recognized by a number of awards, including the 2013 Royal Society of Chemistry Harrison-Meldola Memorial Prize, the 2015 Royal Society of Chemistry Hickinbottom Award and a 2016 Philip Leverhulme Prize.

T06

CATALYTIC CHIRALITY GENERATION: NEW STRATEGIES FOR ORGANIC SYNTHESIS

John Bower

University of Bristol, School of Chemistry, Cantock's Close, BS8 1TS Bristol, United Kingdom

Our group develops new catalysis platforms that enable the efficient generation of chiral building blocks and heterocyclic scaffolds. Current priority areas include: (i) the development of catalytic C-C bond activation processes and associated cycloadditions,[1] (ii) the development of aza-Heck reactions,[2] and (iii) the development of enantioselective alkene hydroarylation reactions.[3] Selected recent highlights will be presented.

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PROF. MARIOLA TORTOSA

AUTONOMOUS UNIVERSITY OF MADRID, Madrid, Spain

Mariola Tortosa obtained her PhD at the Organic Chemistry Institute (CSIC, Madrid, Spain) under the supervision of Professor Fernández de la Pradilla (2005). In 2005, she moved to The Scripps Research Institute in Florida (USA) to work as a Postdoctoral Fellow with Prof. William R. Roush. In 2008 she returned to the Organic Chemistry Institute (Madrid, Spain) as a Research Assistant. In 2011 she started her independent career at the Universidad Autónoma de Madrid (UAM) as an Assistant Professor (Ramón y Cajal Fellow). More recently, she received an ERC-Starting Grant awarded by the European Research Council to work on the project "Design and Applications of Unconventional Borylation Reactions". In 2017, she was promoted to Associate Professor at UAM.

Biologically active compounds (natural products and drugs) are a continuous inspiration for her research which includes asymmetric catalysis, boron chemistry and the development of metal-catalyzed transformations.

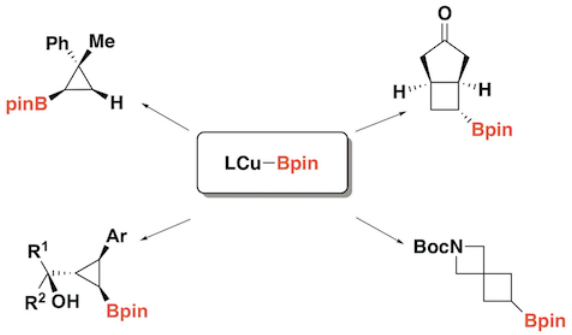
T07

NUCLEOPHILIC BORON FOR THE SYNTHESIS OF FUNCTIONALIZED SMALL RINGS

Mariola Tortosa

Organic Chemistry Department, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Stereodefined small rings are gaining increasing attention in drug discovery because they provide rigidity and at the same time three-dimensionality, expanding new areas of chemical space. In this context, chiral cyclopropyl and cyclobutylboronates are promising synthetic intermediates. They present high configurational stability at the C-B bond and provide a synthetic handle for further stereospecific transformations. Oxidation, amination, homologation, olefination and cross-coupling reactions offer the possibility to access structurally diverse cyclopropanes and cyclobutanes from common intermediates. We have recently used nucleophilic boron species for the preparation of a wide variety of boron-containing small rings, following both enantioselective and stereospecific approaches.[1] These results will be presented in this talk.



Acknowledgements: We acknowledge the European Research Council (ERC, DAUBOR 337776) and MINECO (CTQ2016-78779-R) for financial support.

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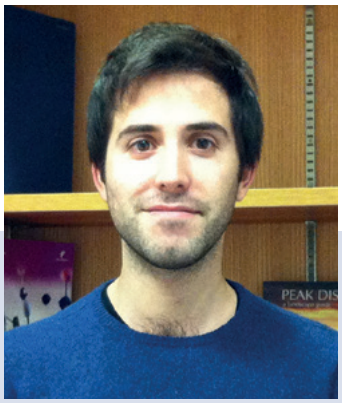


DR DANIELE LEONORI

UNIVERSITY OF MANCHESTER, Manchester, United Kingdom

Daniele obtained his PhD at the University of Sheffield under the supervision of Professor Iain Coldham (2010). After postdoctoral studies with Professor Magnus Rueping (RWTH Aachen University) and with Professor Peter H. Seeberger (Max Planck Institute) he joined the group of Professor Varinder K. Aggarwal FRS as Research Officer (University of Bristol). In 2014 he commenced his independent career as Lecturer in Organic Chemistry at the University of Manchester and was promoted to Reader in 2018.

The group's main research interests are in the area of catalysis and synthetic chemistry, with a focus on the assembly of N-containing molecule.

Daniele was awarded an EPSRC Early Career Fellowship in 2016, the ERC Starting Grant in 2017 and the RSC Harrison-Meldola Memorial Prize in 2018.

T08

PHOTOINDUCED ASSEMBLY OF C–N BONDS

Daniele Leonori

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Nitrogen-containing compounds are a privileged class of molecules, which have applications in medicines, agrochemicals, dyes and materials. This relevance makes the construction of C–N bonds an extremely active area of research.

Nitrogen-radicals are versatile synthetic intermediates that can engage in a broad range of chemical reactions.[1]

However, the difficulties associated with their generation have somewhat thwarted their use in synthetic chemistry.

Development of Photoinduced Radical-Transposition Reactions

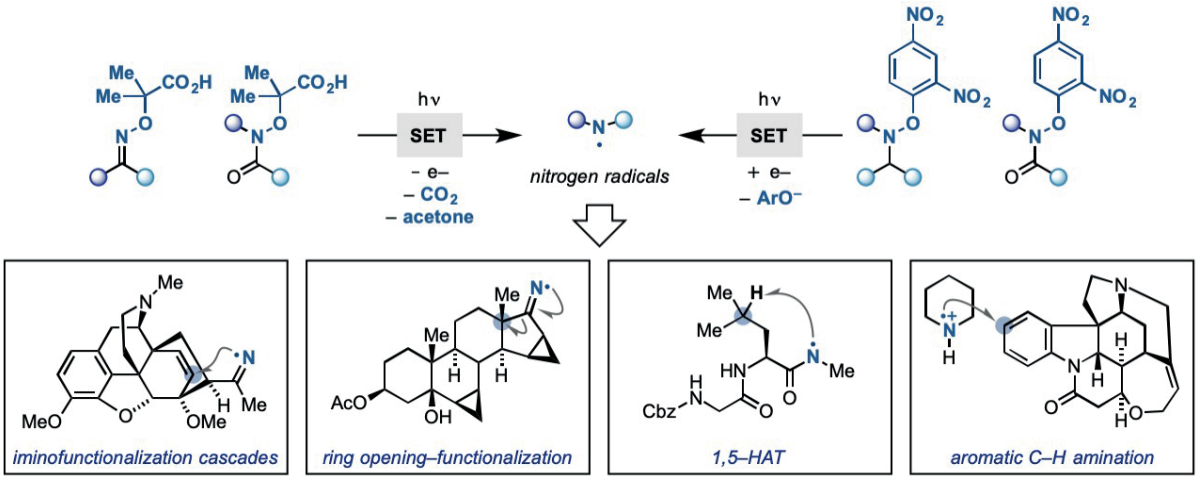
We have developed a class of easy-to-make oximes and hydroxy-amides that upon single-electron oxidation enable access to iminyl and amidyl radicals.[2,3] These species have been used in radical transposition reactions for the site-selective functionalization of unactivated sp^3-carbons.

These strategies have been applied to the deconstruction–functionalization of complex steroids (radical ring-opening)[2] and to the preparation of unnatural amino acids (1,5-HAT).[3]

Development of Photoinduced Aromatic C–H Amination Reactions

Aminated aromatics are a widespread motif in high-value products. In general, these molecules are assembled by Pd- or Cu-catalysed cross-couplings between aryl halides/organoboron and amines. We have developed an umpolung approach where electrophilic amidyl and aminium radicals are generated by photoredox reduction of electron poor *N*-aryloxy-amides and in situ genrated N-Cl-amines.[4,5,6]

These radical species undergo highly selective addition to a broad range of electron rich aromatics thus enabling direct C–H amination.



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DR LASZLO KURTI

RICE UNIVERSITY, Houston, United States

László Kürti was born and raised in Hungary. He received his Diploma from Lajos Kossuth University (now University of Debrecen) where he conducted research in the laboratory of Professor Sándor Antus focusing on the total synthesis of benzofuranoid neolignans. Subsequently he received his Master of Science degree at the University of Missouri-Columbia, working with Professor Michael Harmata on inter- and intramolecular [4+3]-cycloadditions of halogen-substituted oxoallylic cations, and his Ph.D. degree (2006) in synthetic organic chemistry under the supervision of Professor Amos B. Smith III at the University of Pennsylvania where he developed a new method for the construction of highly substituted and strained indoles that was applied in the synthetic studies toward the construction of the complex indole diterpenoid natural products, nodulisporic acids A and B.

While still in graduate school he authored the now popular textbook/reference book "Strategic Applications of Named Reactions in Organic Synthesis" with Barbara Czakó that is now used in dozens of academic institutions and research laboratories worldwide.

In 2006 László joined the group of Professor E.J. Corey at Harvard University as a Damon Runyon Cancer Fellow where he was working on the development of potent antiangiogenic agents inspired by the structure of Cortistatin A. In 2007 he co-authored the book "Molecules and Medicine" with Professor E.J. Corey and Dr. Barbara Czakó. In February 2008, the Professional and Scholarly Division of the American Association of Publishers designated Molecules and Medicine "Best of Physical Sciences and Mathematics". In the Fall of 2010, László and Prof. Corey self-published "Enantioselective Chemical Synthesis: Methods, Logic and Practice" that was warmly received by the community. Now this book is sold by Elsevier/Academic Press.

László began his independent career as an Assistant Professor in the Department of Biochemistry at UT Southwestern Medical Center, Dallas, Texas, but on June 1, 2015 he joined the faculty at Rice University (Houston, Texas); now he is a tenured Associate Professor in the Department of Chemistry. László's laboratory is located in the BioScience Research Collaborative (BRC) building that has state of the facilities and offers many opportunities for collaborations.

The Kürti group focuses on the development of powerful new methods for the expedient enantioselective assembly of highly functionalized biaryls, heterocycles and carbocycles. Thus the group has been exploring several fundamentally new strategies for the transition-metal-free direct: (i) arylation of arenes; (ii); alpha-arylation of ketones, esters and amides; (iii) O-arylation of oximes; (iv) primary amination of arylboronic acids and (v) inter- and intramolecular C(sp2)-H amination of arenes. In-depth experimental and computational studies have already identified the critical factors required for efficient alkyl-aryl, aryl-aryl, O-aryl, N-alkyl and N-aryl bond-formation and led to several innovative and environmentally benign methods for the rapid preparation of structurally diverse arylated carbonyl compounds, functionalized biaryls as well as O- and N-heterocycles. Recently, László has been the recipient of an NSF CAREER Award, Fellowship by the Japan Society for the Promotion of Science (JSPS), the 2014 Amgen Young Investigators' Award as well as the 2015 Biotage Young Principal Investigator Award.

Besides being engaged in research, teaching and writing, in his free time László travels all over the world with his wife and son and enjoys learning about other cultures and people. So far he has visited 37 countries on five continents and 38 states in the US.

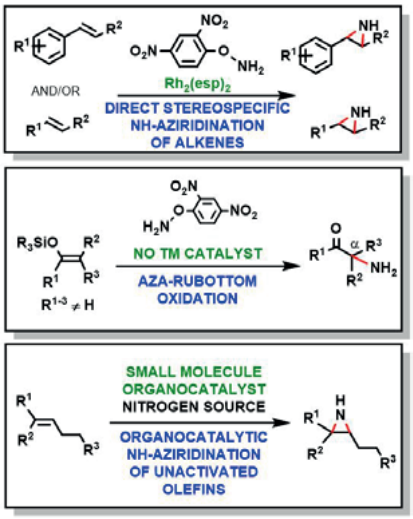
T09

ELECTROPHILIC NITROGEN-TRANSFER PROCESSES

László Kürti

Department of Chemistry, Rice University, Houston, Texas 77030, U.S.A.

Amines and their derivatives are ubiquitous substances since they make up the overwhelming majority of drug molecules, agrochemicals as well as many compounds that are produced by plants and living organisms (i.e., natural products).[1] Aromatic amines appear as substructures in more than one third of drug candidates. Not surprisingly, organic chemists spend a considerable amount of their time with the synthesis and late-stage functionalization of amines that serve as key chemical building blocks for the preparation of biologically active compounds, especially in medicinal chemistry. There is an urgent need for the development of novel carbon-nitrogen bond-forming methods and reagents that expand the toolbox of synthetic organic chemists and enable the environmentally friendly construction of complex molecular structures using the fewest number of chemical steps and generating the least amount waste.



Given this background, the Kürti group actively pursues catalytic C-N bond-forming strategies and processes (i.e., novel modes of nitrogen-transfer) in which the nitrogen-containing group is introduced directly in an unprotected form (i.e., NH_2, NH-alkyl and NH-aryl).[2-6] Despite the recent substantial research effort focused in this area, progress has been limited. This is in part due to a general lack of development of a wide variety of electrophilic aminating agents and catalysts with finely-tuned electronic and steric properties to provide optimal reactivity with a wide range of substrates. The presentation will highlight our latest results on the currently underexplored field of organocatalytic nitrogen-transfers that allow the direct NH-aziridination of isolated/unactivated C=C bonds with high chemoselectivity. These type of processes are intriguing both from a mechanistic and sustainability point of view.

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PROF. STUART CONWAY

UNIVERSITY OF OXFORD, Oxford, United Kingdom

Stuart Conway is a Professor of Organic Chemistry at the University of Oxford, and the E. P. Abraham Cephalosporin Fellow in Organic Chemistry at St Hugh's College, Oxford. He studied Chemistry with Medicinal Chemistry at the University of Warwick before undertaking PhD studies with Professor David Jane and Professor Jeff Watkins FRS at the University of Bristol. Stuart completed post-doctoral studies with Professor Andrew Holmes FRS at the University of Cambridge. In 2003, he was appointed as a Lecturer in Bioorganic Chemistry at the University of St Andrews, in 2008 was appointed as an Associate Professor at Oxford, and in October 2014 he was promoted to Full Professor. Between March and August 2013 Stuart was a Visiting Associate at the California Institute of Technology. Since 2016 he has been an Associate Editor for the Journal of Medicinal Chemistry and he is the President-elect of the RSC Organic Division.

His research focuses on the development of chemical tools to study biological systems.

T10

DESIGN AND SYNTHESIS OF CHEMICAL PROBES FOR BROMODOMAINS

Stuart J. Conway

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK

CREBBP (also CBP or KAT3A) is a transcriptional co-activator and key node in the human protein-protein interactome, binding to over 400 other protein partners.[1] This protein comprises nine domains, which include both an epigenetic 'reader' bromodomain and an epigenetic 'writer' lysine acetyl-transferase (KAT). Small molecule probes for the separate domains are emerging as invaluable tools for dissecting the role played by the individual domains in the overall function of CREBBP.[1] We reported the first high-affinity ligands for the CREBBP bromodomain in 2014.[2,3] These compounds provided a platform for further studies to understand the SAR for CREBBP bromodomain ligands. Here we extend this work to the development of compound **6** (Figure 1), which has a K_d value of 96 nM for CREBBP and is >100-fold selective over BRD4(1). The use of this compound to study the role of CREBBP in HCT116 cells will be discussed. We have also used compound **6** as the basis for the development of a family of macrocyclic CREBBP bromodomain ligands. The design, synthesis, and CREBBP binding affinities of these compounds will be reported.

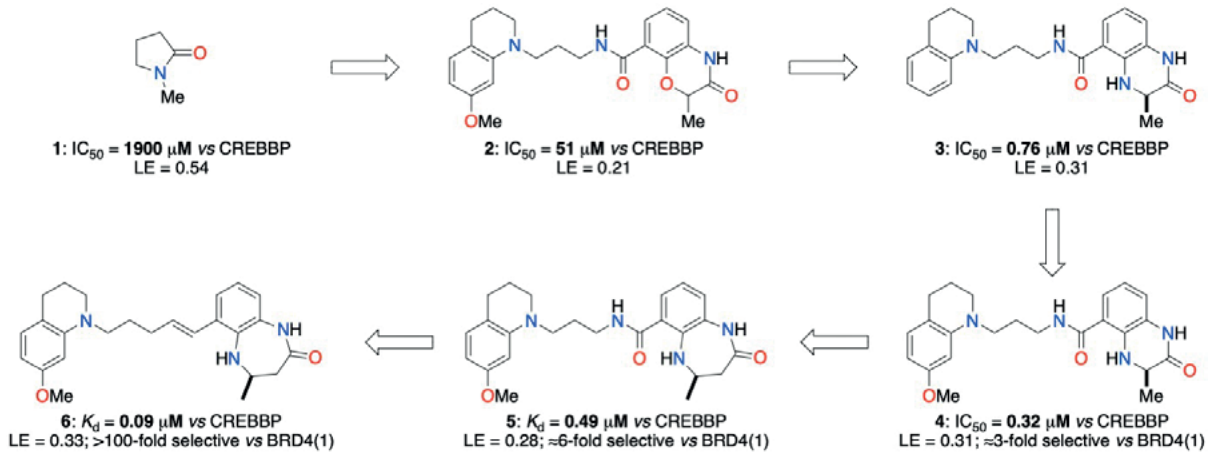

Figure 1. The development of high affnity CREBBP bromodomain ligands.

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DR KIM HUARD

GENENTECH, San Francisco, United States

Dr Kim Huard recently joined Genentech in South San Francisco where she leads chemistry teams on drug discovery programs. In 2008, she graduated from the Université de Montréal with a Ph.D. in organic chemistry where she developed a rhodium-catalyzed carbon-hydrogen bond nitrene insertion methodology. Following her graduate studies, Kim contributed to the total synthesis of the structurally complex natural product daphnipaxinin as a FQRNT postdoctoral fellow at the University of California, Irvine. Kim joined Pfizer in 2010 as a medicinal chemist in the cardiovascular and metabolic disease research unit. Since 2012, she has been leading teams on various drug discovery programs which led to the discovery of three clinical candidates.

Her work involves modulation of different types of biological targets with small molecules as well as targeting specific compound disposition such as liver selective or brain penetrant agents.

T11

A MEDICINAL CHEMIST'S PERSPECTIVE ON SOLUTE CARRIERS: AVOIDING OR TARGETING THEM

Kim Huard

Genentech, Department of Discovery Chemistry, San Francisco, United States

Solute carriers constitute a large family of transmembrane proteins capable of transporting substrates across biological membranes in a controlled manner. Aligned with specific roles for each of the family members, their expression profiles are as diverse as the nature of their substrates, which ranges from a single atom to large and complex molecules. In the pharmaceutical industry, solute carriers have been a rich source of disease-associated proteins. From a small molecule medicinal chemist's standpoint, the solute carrier family is of importance not only as pharmacological targets but also due to their potential impact on compound pharmacokinetic and toxicity profiles. This is now generally recognized by the scientific community and in some instances, guidance from regulatory agencies is in place to reduce the associated risks. However, our understanding and characterization of the various transporters and their potential impacts on drug discovery projects are still evolving and in vitro assays and modeling have been developed only for a small fraction of the family. In this presentation, I will provide a medicinal chemist's perspective on the solute carrier family with a focus on hepatic transporters, some of the most characterized members. A summary of current assays and tools will be provided with examples of how they were used to identify compounds with the desired profile, including liver targeted analogs.

DR ERIK HETT

MERCK EXPLORATORY SCIENCE CENTER, Boston, United States

Dr Erik Hett received his Ph.D. from Harvard University in the lab of Dr. Eric Rubin, studying protein-protein interactions important for regulating cell division in mycobacteria. His postdoctoral research was conducted in the lab of Dr. Deborah Hung at Harvard, Broad Institute and Massachusetts General Hospital, where he conducted phenotypic high-throughput screens and utilized chemoproteomics for target ID. He previously was a chemical biologist in the MedChem Department at Pfizer and led a chemical biology team in the mechanisms and pathways group at Biogen. He is currently the Head of Experimental and Chemical Biology at Merck's Exploratory Sciences Center in Cambridge, MA.

T12

A CHEMICAL APPROACH TO MAP PROTEIN INTERACTIONS AT THE CELL SURFACE

Rob Oslund, Tamara Reyes Robles, Jake Tomlinson, Kelly Crotty, Samantha O'Hara, David Perlman, Cory White, Daria Hazuda, Lee Roberts, Grazia Piizzi, Erik Hett, Niyi Fadeyi

Merck Exploratory Science Center, 320 Bent Street, 4th Floor, Cambridge, MA, USA

Membrane proteins play key roles in recognition, communication, and signal transduction. We have developed both enzyme-based and small molecule-based approaches to label proteins in proximity to proteins of interest on living cells. This novel technology has been applied to different protein targets and cell types with the goal of identifying proteins of biological importance relevant to drug discovery.

DR LAURENT SCHIO

SANOFI, Vitry sur Seine, France

Laurent Schio is currently head of Integrated Drug Discovery of Sanofi in France. He supervises groups of medicinal chemistry, drug design, structural biology, screening and data management. He is organic chemist by training. He obtained his PhD degree from the University of Rennes (Britany-France) in 1990 in Dr René Gree's laboratory (iron tricarbonyle complexes). He performed then a postdoctoral stage in Pr. Joshua Rokach's laboratory (synthesis of isoprostaglandins) in the Florida Institute of Technology (Melbourne). He joined then Sanofi (Roussel-Uclaf) in 1991.

His main therapeutic domains of expertise are the anti-infective and oncology areas and contributed to the discovery of several clinical candidates (Aminocandin, cMET, PI3Kb, SERD...).

He is author of more than 25 publications, co-inventors in 20 patents and has realized more than 20 oral presentations worldwide. He is currently member of the Sanofi French Hub and the Oncology Discovery Boards.

T13

FROM FRAGMENTS TO ANTIBODY DRUG CONJUGATES IN EMERGING ONCOLOGY TARGETED THERAPIES

Laurent Schio

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Over the last two decades, more efficient and safer therapies have emerged to treat cancer patients based on a better understanding of the drivers which trigger tumorigenesis. Genetic alterations assessment in tumors can support patient stratification for more straightforward plans of development and higher response rates in clinical trials. In this presentation we will overview three internal drug discovery projects which have been developed applying this personal medicine paradigm. We will first describe a breakthrough hit discovery approach which proved to be efficacious to tackle a specific mutant of KRAS, the genetic cause of a devastating lung cancer type. KRAS used to be reluctant to any research effort in the past to identify specific inhibitors. We will also indicate the discovery strategy approach which was followed to produce SAR439859 a full degrader of the estrogen receptor alpha for ER+ breast cancer treatment. Preliminary clinical results of this development candidate will be highlighted. Finally, we will elaborate on the emergence of Antibody Drug Conjugates (ADC) as new anti-cancer modalities which combine potency of cytotoxic agents and targeted vectorization towards tumors. Preclinical and clinical efficacy studies of SAR408701, an anti-CEACAM5 ADC, will be given.

PROF. JONATHAN BAELL

MONASH UNIVERSITY, Parkville, Australia

Jonathan Baell obtained his PhD in 1992 under Professors Peter Andrews and Paul Alewood at the Victorian College of Pharmacy (now MIPS) and went on to become a senior research scientist in CSIRO, Australia's national scientific research organisation. Then, after a decade as head of medicinal chemistry at the Walter and Eliza Hall Institute of Medical Research (WEHI), he was appointed as a research professor at MIPS.

His interests are in the design of quality of HTS libraries, medicinal chemistry hit-to-lead and lead optimization, and computer-aided peptidomimetic design. Apart from his publications, he has over 40 granted pharmaceutical patents with compounds in various stages of development and clinical trial.

In 2005 he was awarded the 2004 RACI Biota Medal, a national award for excellence in medicinal chemistry for an early to mid-career researcher, followed by the Adrien Albert Medal for sustained medicinal chemistry excellence, in 2018. He sits on numerous scientific and editorial advisory boards, including Journal of Medicinal Chemistry, and is co-Senior Editor of Future Medicinal Chemistry.

T14

AWARENESS OF PAINS (PAN ASSAY INTERFERENCE COMPOUNDS) CAN ACCELERATE THE DRUG DISCOVERY PROCESS

Jonathan Baell

Monash Institute of Pharmaceutical Sciences (MIPS), Melbourne, Australia; Email: jonathan.baell@monash.edu

In 2010 we published our disclosure of pan-assay interference compounds (PAINS).[1] The subject matter appeared to be timely and this paper now numbers some 1500 citations and its subsequent higher level 2014 commentary[2] some 500 citations. PAINS are nuisance compounds that can interfere in assay signaling at many levels. Awareness of PAINS can indirectly accelerate the drug discovery process. Here we will discuss this notion and briefly touch on some medicinal chemistry projects, from protein-protein interactions[3] to enzymes[4,5] , whose successful outcomes can indirectly be attributed to awareness of the PAINS concept.

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DR KARL-HEINZ BARINGHAUS

SANOFI, Frankfurt, Germany

Karl-Heinz Baringhaus obtained his Ph.D. in synthetic organic chemistry at the University of Muenster. After a postdoctoral fellowship at Stanford University he joined Hoechst AG where he was working in Medicinal Chemistry. In 2000 he became Head of Computational Chemistry at Aventis Pharma. From 2005 to 2010 he was Director of Drug Design at Sanofi-Aventis Pharma Deutschland GmbH. In 2010 he was promoted to Head of Structure, Design & Informatics consisting of Computational Biology & Bioinformatics, Computer-aided Drug Design, Scientific Computing & Data Management as well as Structural Biology. In 2012 Karl-Heinz was appointed R&D Site Director at Sanofi in Germany.

T15

ARTIFICIAL INTELLIGENCE IN ADMET MODELING AND COMPOUND PROFILING

Karl-Heinz Baringhaus, Gerhard Hessler, Hans Matter, Friedemann Schmidt, Jan Wenzel

Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, Building H831, 65926 Frankfurt am Main, Germany

Modern Drug Design plays a pivotal role in identification and optimization of suitable lead compounds aiming preclinical candidates. Application of Artificial Intelligence in this field offers excellent opportunities for compound classification, ADMET modeling and *in silico* profiling.

This presentation covers several aspects of artificial intelligence in modern Drug Design. For example, regression-based decision trees as well as neural networks are used to model large data sets of ADMET properties. Both techniques yield high quality models which are applied in the design of suitable lead compounds and preclinical candidates.

Deep learning in chemical and biological space offers new opportunities for *in silico* profiling of molecules. Out of a few thousand biological assays and several million compounds we build predictive models for approximately 500 targets of interest. All models are thoroughly validated including a validity domain estimation (VDE). The combination of our models with CTlink is very powerful in selecting the most attractive hit series out of an HTS run and in the identification of potential side effects of lead series prior to subsequent optimization. Compound repurposing as well as polypharmacology of compounds are growing needs and can be addressed by both methods.

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ChemMedChem Lecture

PROF. MARIA LAURA BOLOGNESI

UNIVERSITY OF BOLOGNA, Bologna, Italy

Maria Laura Bolognesi is Professor of Medicinal Chemistry, Director of the Chemistry and Pharmaceutical Technologies degree program and Rector Delegate for Latin American International Relations at the University of Bologna. She obtained her PhD under the mentorship of Professor Carlo Melchiorre in 1996 and carried out postdoctoral work at the University of Minnesota with Professor Philip S. Portoghese.

Her research explores the development of small molecules in the neurodegenerative and neglected tropical disease therapeutic areas. Maria Laura was awarded the positions of Distinguished Visiting Professor at the Complutense University of Madrid in 2009, Pesquisador Visitante Especial at the University of Brasilia in 2014 and Professeur Invité at Université Caen Normandie in 2018. She is an Associate Editor of Journal of Medicinal Chemistry and serves in the Advisory Board of the European Federation of Medicinal Chemistry.

T16

SUSTAINABLE BY DESIGN ANTI-TRYPANOSOMATID SMALL MOLECULES: AN ASPIRATIONAL GOAL FOR MEDICINAL CHEMISTRY

Maria Laura Bolognesi

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Although the progress made, poverty-related trypanosomatid diseases continue to be an ongoing challenge. The many drawbacks of currently available treatments, especially in terms of low access, high toxicity and complicated administration regimens, calls for drug discovery endeavors focused on sustainable principles.[1] These should guide all involved stakeholders, including medicinal chemists. Considering the many nuances of medicinal chemistry contexts of sustainability, in this talk I will discuss the contribution of our team towards the aspirational goal of ensuring a more sustainable drug discovery pipeline for these diseases.

We envisioned that a strategy exploiting privileged-structures-based phenotypic libraries might be useful to identify hits in a cost- and time-effective manner. Thus, we generated a focused library by fast assembling phenothiazine, biphenyl and phenylpiperazine privileged fragments via a Huisgen cycloaddition. The library was screened for activity against *Trypanosoma brucei*and *cruzi*, *Leishmania infantum*and *donovani*, for selectivity against mammalian cells, and for ADME-Tox properties. Despite the small library size, this strategy led to the successful identification of interesting hits with promising profiles.[2]

Another extraordinary possibility is the development of new drugs based on food industry wastes as sustainable starting materials. Towards this aim, we developed a series of novel *T. brucei*hits obtained by combining a 2-phenoxy-1,4-naphthoquinone scaffold with phenolic constituents from the cashew nut shell liquid (CNSL), a by-product and a pollutant from cashew nut processing factories.[3]We envisage that such compounds, easily obtained from a waste material produced in high quantity in the endemic countries, might be ethically, environmentally and economically sustainable starting point for the development of new anti-trypanosomatid drugs. These two examples, although preliminary, hopefully serve to illustrate that it is possible to address pressing pharmaceutical sustainability challenges even at a very early discovery phase and within an academic context.

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DR OLA ENGKVIST

ASTRAZENECA, Mölndal, Sweden

After he completed his PhD in Computational Chemistry at the University of Lund and postdoctoral research at the University of Cambridge and the Czech Academy of Sciences, he joined AstraZeneca in 2004. He currently leads the Discovery Sciences Computational Chemistry team within the IMED Biotech Unit, providing computational solutions for drug discovery.

He is passionate about pushing the boundaries of using artificial intelligence and machine learning in drug discovery. A key focus for him has been on building both the team within IMED and collaborating with external experts to advance innovation in drug design and synthesis.

Through a pioneering collaboration with the University of Muenster, his team demonstrated the first application of recurrent Neural Networks to molecular design which has been published in two recent, highly-cited articles. This methodology allows them to design novel drug molecules using machine learning to navigate the breadth of chemical space and to exploit their vast knowledge base.

T17

ARTIFICIAL INTELLIGENCE IN de Novo MOLECULAR DESIGN

Ola Engkvist

AstraZeneca, Pepparedsleden 1, 431 50 Mölndal, Sweden

Artificial intelligence is underway to transform the society through technologies like self-driving cars. Also, in drug discovery machine learning and artificial intelligence methods has received increased attention. [1] The increased attention is not only due to methodological progress in machine learning and artificial intelligence, but also progress in automation for screening, chemistry, imaging and -omics technologies, which have generated very large datasets suitable for machine learning.

While machine learning has been used for a long time in drug design, there has been two exiting developments during the last years. One is the progress in synthesis prediction, where deep learning together with fast search methods like Monte Carlo Tree Search has been shown to improve synthetic route prediction as exemplified by a recent Nature article. [2] In this talk I will focus on the second development, which is applying deep learning based methods for *de novo* molecular design. It has always been the dream of the medicinal and computational chemist to be able to search the whole chemical space of estimated 10^{60} molecules. This would be a step change compared to search enumerable chemical libraries of perhaps 10^{10} compounds. Methods to search the whole chemical space through generative deep learning architectures has been developed during the last 3-years. In the presentation there will be a focus de novo generation of molecules with the Recurrent Neural Network (RNN) architecture. The basis will be described and exemplified of how molecules are generated. After the concept has been introduced it will be described how the method is used within drug design projects at AstraZeneca. Current limitations will be discussed in conjunction with mitigation strategies to further enhance the potential of RNN based molecular de novo generation.

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PROF. NEIL GARG

UNIVERSITY OF CALIFORNIA, Los Angeles, United States

Neil Garg received a B.S. in Chemistry from New York University where he did undergraduate research with Professor Marc Walters. He obtained his Ph.D. in 2005 from Caltech studying under the direction of Professor Brian Stoltz. Garg then joined Professor Larry Overman's laboratory at the University of California, Irvine as an NIH Postdoctoral Scholar. Garg joined the faculty at UCLA in 2007. He was promoted to Associate Professor in 2012, and then to Full Professor in 2013. He has served as Vice Chair for the Department of Chemistry and Biochemistry (2012-2016) and currently serves as Faculty-in-Residence in the UCLA undergraduate community. In 2018, Garg was appointed as the inaugural holder of the Kenneth N. Trueblood Endowed Chair in Chemistry and Biochemistry.

T18

AMIDES AND CHEMICAL EDUCATION AS VEHICLES FOR INNOVATION

Neil Garg

UCLA, Department of Chemistry & Biochemistry, Los Angeles, CA 90095, United States

This presentation will focus on two key areas of interest in Professor Neil Garg's laboratory: research in the area of amide cross-coupling reactions and innovations in the area of chemical education.

The first part of the lecture will focus on my laboratory's recent efforts to cleave amide carbon–nitrogen bonds using nickel catalysis. Amides have long been considered 'stable' or relatively unreactive functional groups. Accordingly, the synthetic chemistry of amides, particularly involving amide C–N bond cleavage, has remained underdeveloped. The lecture will describe our entryway into amide C–N bond cleavage, in addition to several catalytic cross-coupling methodologies we have now developed, such as the nickel-catalyzed esterification of amides and the Suzuki–Miyaura coupling of amides. These studies demonstrate that amides, despite classically being considered 'unreactive', can be activated using nickel-catalysis and exploited as valuable synthetic building blocks.

In addition, initiatives in the realm of chemical education will be discussed. Organic chemistry has maintained a bad reputation for decades, despite having a tremendous impact on our everyday lives. It has remained a notorious "weed-out" class for decades – striking fear in the hearts of students – and has long been viewed as a gatekeeper course for those interested in pursuing a career in medicine. This presentation will showcase recent efforts that have helped to transform organic chemistry into one of the most popular classes on the UCLA campus. Educational initiatives, including organic chemistry music videos and online tutorials, will be discussed.

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Twitter: @garglab

DR MALIN LEMURELL

ASTRAZENECA, Gothenburg, Sweden

Malin Lemurell achieved her PhD at the Gothenburg University in 1999 in organic chemistry, specialized on bio-catalyzed asymmetric transformations. After post-doctoral studies on metal catalyzed asymmetric oxidation at The Scripps Research Institute in California with Prof. Barry Sharpless, she continued her career in medicinal chemistry as scientist and later leader at AstraZeneca, Gothenburg, Sweden. Malin is the inventor of 13 patents, incl patents behind the launched medicine Elobixibat and currently two other compounds in Phase II clinical development.

Her research field is Medicinal Chemistry with long experience in the Cardiovascular, Renal and Metabolism disease areas and with special interest in drug design, innovations in the interface of chemistry and biology including new chemical modalities and targeted drug delivery, as well as development of drug hunters of the future.

T19

DISCOVERY OF AZD5718, A NOVEL 5-LIPOXYGENASE ACTIVATING PROTEIN (FLAP) INHIBITOR

Malin Lemurell (1), Daniel Pettersen (1), Johan Ulander (2), Martin Hayes (3), Carl Whatling (1), Marianne Swanson (1), Johan Broddefalk (1), Hans Emtenäs (2), Eva-Lotte Lindstedt (1)

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2) Pharmaceutical Sciences, BioPharmaceuticals R&D, AstraZeneca, SE-431 83 Gothenburg, Sweden
3) Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, SE-431 83 Gothenburg, Sweden

5-lipoxygenase activating protein (FLAP) is essential for the activity of 5-LO, the key first step in leukotriene biosynthesis. AZD5718 is a novel oral FLAP inhibitor aiming to reduce cardiovascular mortality and morbidity in coronary artery disease (CAD) patients by attenuation of proinflammatory and vasoactive leukotriene production. The recently concluded Phase 1 study demonstrates that AZD5718 is safe & tolerated, with a pharmacokinetics amenable for QD oral dosing. Paired with dose dependent and potent target engagement on both arms of the 5-LO pathway, the Phase 2a study started 2017. Herein we will disclose the medicinal chemistry discovery and development of AZD5718 which entirely originates from a novel in-house chemical series. The key learnings from the Medicinal Chemistry and drug discovery strategies undertaken will be discussed.

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PROF. SABINE FLITSCH

UNIVERSITY OF MANCHESTER, Manchester, United Kingdom

Sabine has a long-standing interest in the application of biocatalysis to organic synthesis. More recently, she has developed multistep cascade reactions mediated by enzymes, both in cell free and whole cell systems for the stereoselective synthesis of carbohydrates and amines.

Sabine obtained a Diploma in Chemistry from the University of Muenster, Germany and a DPhil degree from Oxford University under the supervision of Sir J E Baldwin. She spent three years of postdoctoral studies with Professor H G Khorana at MIT before returning to the UK to pursue her academic career at the Universities of Exeter, Oxford, Edinburgh and now Manchester, where she has held a Chair since 2004.

T20

DESIGN AND IMPLEMENTATION OF DE NOVO BIOSYNTHETIC CASCADES

Sabine Flitsch

University of Manchester, The Manchester Institute of Biotechnology, 131 Princess Street, M1 7DN Manchester, United Kingdom

The combination of sequential biocatalytic reactions in non-natural synthetic cascades is a rapidly developing field and leads to the generation of complex valuable chemicals from simple precursors. As the toolbox of available biocatalysts continues to expand, so do the options for biocatalytic retrosynthesis of a target molecule, leading to new routes employing enzymatic transformations. The implementation of such cascade reactions requires careful consideration, particularly with respect to whether the pathway is constructed *in vitro* or *in vivo*. This lecture will showcase three successful *de novo cascades* and discuss the relative merits of *in vitro*, *in vivo* or hybrid approaches to building biocatalytic cascades and analytical challenges. Biocatalysts were obtained either directly from genomic libraries, or by re-design of enzyme activity to suit required substrate specificity and selectivity. A particularly important reaction class for enzyme cascades is C-H activation, which allows for the stereoselective functionalisation of simple organic substrates and biological feedstocks, such as fatty acids.

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PROF. ALOIS FÜRSTNER

MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG, Muelheim an der Ruhr, Germany

Alois Fürstner studied chemistry in Austria where he obtained his doctoral degree in 1987 from the Technical University of Graz (Prof. H. Weidmann). After a postdoctoral stint with the late Prof. Oppolzer in Geneva, Switzerland, and a Habilitation in Graz, he joined the Max-Planck-Institut für Kohlenforschung, Mülheim, Germany, in 1993 as a group leader. In 1998, he was promoted to the rank of Director of this Institute and served as its Managing Director in 2009-2011 and 2016-2017.

His scientific interests relate to organometallic chemistry and homogeneous catalysis, including applications thereof to target oriented synthesis. Long term projects are focused on alkene- and alkyne metathesis, pi-acid catalysis based on platinum and gold, iron catalyzed cross coupling, and carbene chemistry in general. These methods opened concise and flexible entries into numerous bioactive natural products (alkaloids, macrolides, prostaglandins, glycolipids).

T21

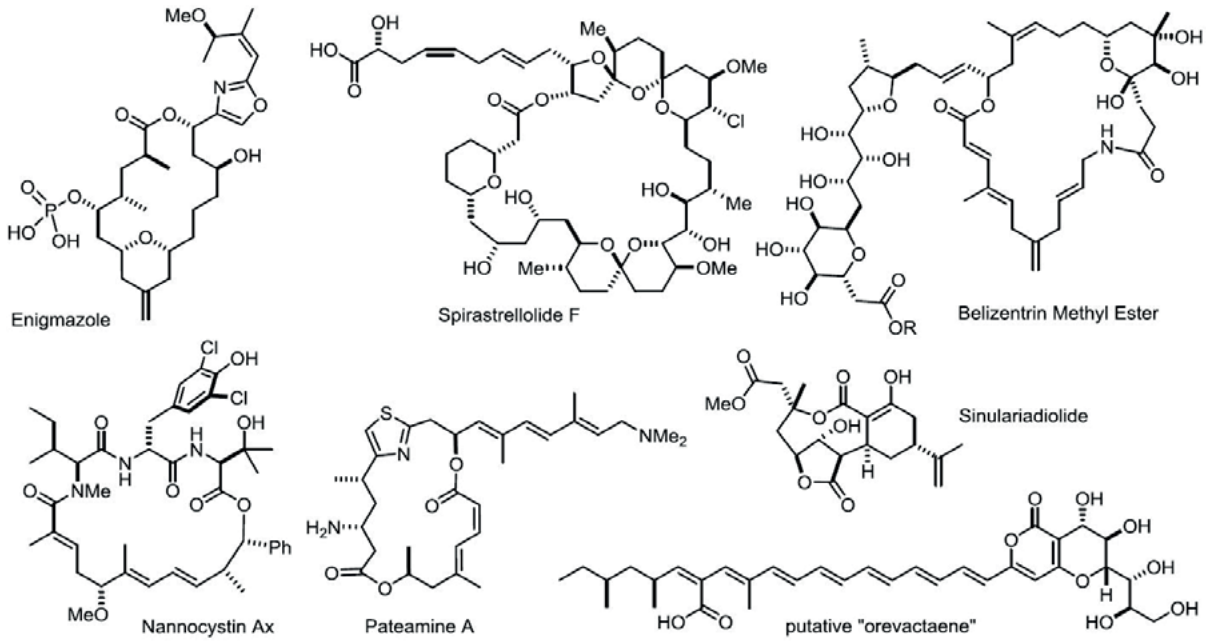
CATALYSIS FOR TOTAL SYNTHESIS

Alois Fürstner

Max-Planck-Institut für Kohlenforschung, 45470 Mülheim/Ruhr, Germany

In this lecture I intend to discuss the development of new catalytic transformations and show their impact on logic and practice of target-oriented synthesis. The focus will be on recent advances in alkyne functionalization with the aid of carbophilic catalysts [1,2], as well as on iron catalysed cross coupling reactions [3].

These methods opened access to a host of target molecules of different chemical estates, exhibiting promising biological activities [4-10]. In some cases, our synthesis campaigns led to the revision of the structures and/or bioactivities originally proposed by the isolation teams.



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PROF. GEORGIOS VASSILIKOGIANNAKIS

UNIVERSITY OF CRETE, Heraklion, Greece

Georgios Vassilikogiannakis is Full Professor of Organic Chemistry at the Department of Chemistry of the University of Crete.

He obtained his Ph.D. (1998) in Physical Organic Chemistry with Prof. M. Orfanopoulos from the University of Crete (Greece). From 1999-2002, he was a postdoctoral fellow at the Scripps Research Institute (California, U.S.A.) in the group of Prof. K. C. Nicolaou.

In 2002 he started his academic career at the University of Crete initially as an Assistant Professor. In 2008, he was promoted to Associate Professor, and, in 2013, to Full Professor.

He is the recipient of an ERC Consolidating grant and an ERC Proof of Concept grant.

His research interests are in the field of Sustainable Synthetic Organic Chemistry with a particular focus on: a) The development and application of new green synthetic methodologies that use Singlet Oxygen as a green oxidant and cascade reaction facilitator and b) the continuous flow photochemisty.

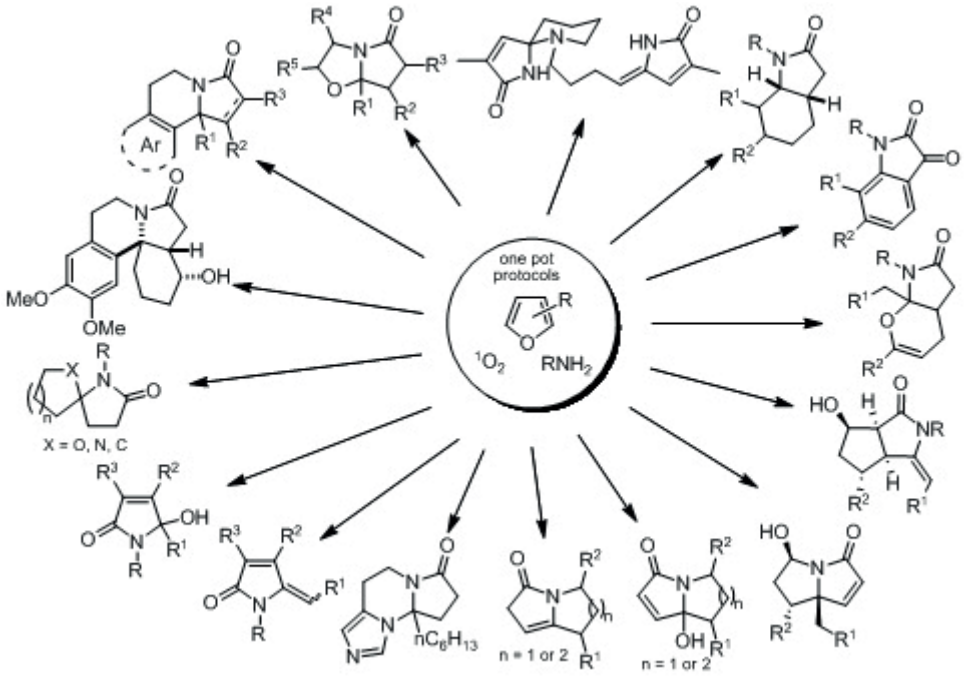
T22

DEVELOPMENT AND APPLICATION IN FLOW OF SUSTAINABLE SYNTHETIC METHODOLOGIES THAT USE SINGLET OXYGEN AS GREEN OXIDANT AND CASCADE REACTION FACILITATOR

Dimitris Kalaitzakis, Georgios Ioannou, Manolis Sofiadis, Tamsyn Montagnon, Georgios Vassilikogiannakis

Department of Chemistry, University of Crete, Vasilika Vouton, 71003, Iraklion, Crete, Greece

An overview of sustainable synthetic methods that use singlet oxygen as green oxidant and cascade reaction facilitator will be presented.[1] The development and application of a novel continuous flow photoreactor which is based on the singlet oxygen chemistry in pneumatically generated aerosols (nebula) for highly productive photooxidations will be also presented.[2]



Acknowledgements: The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 277588. We thank the Greek General Secretariat of Research and Technology for matching (reward) funds (KA: 4143 and 4154). We also thank the Alexander S. Onassis Public Benefit Foundation for the Ph.D. fellowship of Manolis Sofiadis (G ZM 063-1/2016-2017).

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DR JESÚS ALCÁZAR

JANSSEN RESEARCH & DEVELOPMENT, Toledo, Spain

Jesús Alcázar studied in Universidad de Castilla-La Mancha in Ciudad Real where he got his bachelor degree in 1990 and Ph. D. in 1996. As Ph. D. student he stayed for 6 months at the Royal Danish School of Pharmacy (Copenhagen, Denmark) under the direction of Prof. Michael Begtrup.

In 1995 he joined Janssen-Cilag at the research center in Toledo. Currently he is Senior Principal Scientist at Janssen Research and Development. In this position he is involved in the implementation of novel technologies in Drug Discovery in Toledo and in collaboration with other J&J sites worldwide. In this role he has led the successful implementation of 3 different technologies: microwave, H-CUBE and Flow chemistry, technologies that are currently a common tool at J&J worldwide. In addition, he has successfully applied these technologies to Medicinal Chemistry programs with 4 compounds selected as clinical candidates.

In the field of catalysis, he has made important contributions in the field of supported catalysis as well as the discovery of light induced cross coupling reactions.

He has been author of 5 book chapters and around 65 articles. He is inventor in around 35 patent applications.

T23

FLOW CHEMISTRY AND PHOTOCHEMISTRY AS A TOOL FOR DRUG DISCOVERY

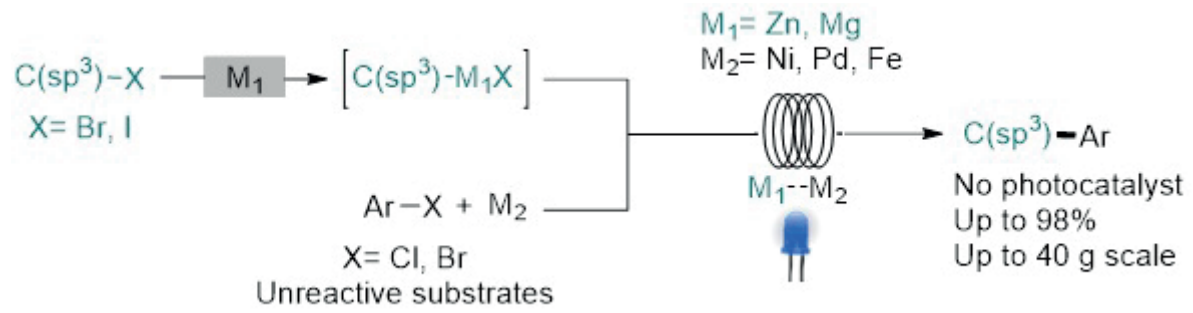
Jesús Alcázar

Discovery Chemistry, Janssen Research & Development, Rio Jarama 75A, 45007 Toledo, Spain

Continuous flow chemistry has recently emerged as a novel chemical tool that can help synthetic chemists to combine efficiency and sustainability. Implementation of this technology in the Pharma industry started more than 10 years ago in Development, where its main advantages (High control of the reaction variables, heat and mass transfer; access to novel process windows, easier reproducibility and scalability) clearly matched the needs of the industry at this level.

However, this technology did not attract much attention in Discovery, where speedy preparation of a pool of target compounds is usually required. Many Medicinal Chemists are still wondering what value Flow Chemistry adds over traditional batch parallel approaches and they foresee its potential application limited to resolving scaling up issues.

In order to introduce this technology in a Drug Discovery setting, different methodologies have been developed to overcome current limitations in Drug Discovery. For example, preparation of organometallic reagents just flowing halogenated derivatives through a column filled with the corresponding metal (zinc or magnesium) and their application to get compounds with increase C(sp3) ratios and better pharmacokinetic properties. More recently, the addition of photochemistry in flow has allowed medicinal chemists to access new chemical space in multigram amounts, overcoming the limitations of batch. These flow approaches are currently having an impact at all levels of the Drug Discovery process in our company, from Hit to Lead to Late Lead Optimization.



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DR HARALD ENGELHARDT

BOEHRINGER-INGELHEIM, Vienna, Austria

Current title and position: Principal Scientist Medicinal Chemistry, Leader of a research lab

Research field: Oncology

Professional experience and education:

Since 01/2003	Project leader for international and interdisciplinary research projects
Since 01/2001	Principal Scientist Medicinal Chemistry at Boehringer Ingelheim RCV GmbH & Co KG
05/1998 – 12/2000	Lab Scientist at Boehringer Ingelheim Pharma KG
08/2008 – 12/2013	PhD thesis under the supervision of Prof. Dr. R. Leurs and Prof. Dr. E. E. J. Haaksma with the title "Design and preparation of new ligands interacting with the Histamine H4 receptor" at the VU University Amsterdam and at Boehringer Ingelheim RCV GmbH & Co.
10/1997 – 02/1998	Diploma thesis under the supervision of Prof. Dr. T. Herold and Dr. L. Kisielowski

T24

START SELECTIVE AND RIGIDIFY: THE DISCOVERY PATH TOWARDS THE NEXT GENERATION OF EGFR TYROSINE KINASE INHIBITORS

Harald Engelhardt (1), Dietrich Böse (1), Mark Petronczki (1), Dírk Scharn (1), Gerd Bader (1), Anke Baum (1), Andreas Bergner (1), Eugene Chong (3), Sandra Döbel (1), Georg Egger (1), Christian Engelhardt (1), Peter Ettmayer (1), Julian E. Fuchs (1), Thomas Gerstberger (1), Nina Gonnella (2), Andreas Grimm (1), Elisabeth Grondal (1), Nizar Haddad (3), Barbara Hopfgartner (1), Roland Kousek (1), Mariusz Krawiec (2), Monika Kriz (1), Lyne Lamarre (1), Joyce Leung (3), Moriz Mayer (1), Nitin Patel (3), Biljana Peric Simov (1), Jonathan Reeves (3), Remate Schnitzer (1), Andreas Schnek (1), Bernadette Sharps (1), Flavio Solca (1), Heinz Stadtmüller (1), Zhulin Tan (3), Tobias Wunberg (1), Andreas Zoephel (1), Darryl B. McConnell (1)

1) Boehringer Ingelheim RCV GmbH & Co KG, Doktor-Boehringer-Gasse 5-11, 1120 Vienna, Austria
2) Material and Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877, United States
3) Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877, United States

The epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, acts as an oncogenic driver in a subset of lung tumors. Tumors carrying the two most frequent primary activating EGFR mutations, del19 or L858R, are sensitive to treatment with EGFR tyrosine kinase inhibitors (TKIs). While tumor responses to EGFR TKIs are accompanied by marked tumor shrinkage, the response is usually not durable. Most patients relapse within two years of therapy often due to acquisition of additional mutation in EGFR that confer resistance to TKIs. The EGFR gatekeeper mutation T790M exerts resistance to 1st and 2nd generation EGFR TKIs, while the EGFR mutation C797S renders 3rd generation EGFR TKIs ineffective. Crucially, oncogenic EGFR harboring both resistance mutations, T790M and C797S, can no longer be inhibited by any approved EGFR TKI.

The discovery of **BI-4020**, a non-covalent, EGFR^{wt} sparing, macrocyclic TKI which potently inhibits the most common primary oncogenic EGFR mutant, del19, and shows tumor regressions in the cross-resistant PC-9 (EGFR$^{del19\ T790M\ C797S}$) triple mutant mouse xenograft model, will be presented. Key to the discovery was the identification of a highly selective but moderately potent benzimidazole followed by complete rigidification of the molecule through macrocyclisation. The profile of **BI-4020** would allow the first time to treat EGFR^{del19} NSCLC patients in the 3rd and 2nd line settings after emergence of the T790M and C797S mutations.

DR KONRAD BLEICHER

F.HOFFMANN-LA ROCHE LTD, Basel, Switzerland

Konrad Bleicher holds a Ph.D. in Organic Chemistry which he received from the Tübingen University in Germany. He started his professional career at Sandoz/ Novartis (Switzerland & US) where he gained experience in the area of Combinatorial Chemistry before joining Roche as a scientist in the CNS chemistry department. Since then he has been holding various positions in the Small Molecule Medicinal Chemistry area (Hit ID, Lead ID & Lead Optimization). In 2009 Dr. Bleicher was nominated "Peptide Area Head", overseeing the peptide chemistry activities in Pharma Early Research & Development. Since 2016 he is responsible for the RNA Therapeutics Chemistry strategy and platform development in Roche Basel.

He is the author of over 60 patents and publications and an invited speaker for various international conferences.

T25

RNA THERAPEUTICS: NEW CHEMICAL MODALITIES BECOMING A THERAPEUTIC REALITY

Konrad Bleicher (1), M. Li (1), A. Schäublin (1), E. Funder (2), J. Duschmalé (1)

1) RNA Therapeutics, F. Hoffmann-La Roche Ltd., Roche Innovation Center Basel, Switzerland, konrad.bleicher@roche.com
2) RNA Therapeutics, Roche Innovation Centers, Copenhagen, Denmark

Conceptually, RNA based molecules have been introduced as a potential therapeutic modality already back in 1978 by Zamecnik and Stephenson, demonstrating *in vitro* that the protein biosynthesis machinery can be modulated through Watson-Crick based interactions between a target RNA (Rous sarcoma virus) and a complementary oligonucleotide strand, in this particular case a 13-mer DNA oligonucleotide. Twenty years after this pioneering study, the first therapeutic Antisense Oligonucleotide (ASO) was approved by the FDA for the treatment of cytomegalovirus-induced retinitis in immunocompromised AIDS patients (Vitravene). Despite this successful launch, the field has been in turmoil and it took fifteen more years for yet another important breakthrough with the launch of Kynamro for the treatment of homozygous familial hypercholesterolemia. While this product was commercially not very successful, it demonstrated that indeed the systemic administration of such a modality is feasible and clinically functional. Since then, a couple of drugs have been marketed, which also go beyond RNase-H mediated RNA knockdown, and a rather impressive clinical portfolio has been built for different targets and indications.

Since the first published study by Zamecnik and Stephenson, it has been recognized that oligonucleotides need to be chemically modified to induce functional activity and over the years a broad range of chemical modifications have been investigated with the main purpose to positively modulate the pharmacokinetic profile of RNA drug candidates. Unarguably, the most fundamental invention in this respect was the introduction of the phosphorothioate internucleoside linkage, with most of the current oligonucleotide drugs and clinical assets carrying such a modification to various extents. While thereby introducing a chiral centre, recent developments in oligonucleotide chemistry now make the synthesis of fully stereodefined phosphorothioate ASOs possible, by generating these phosphorothioate linkages in an enantioselective fashion, allowing us to investigate the drug properties of single molecules rather than otherwise huge mixtures of diasatereoisomers.

This presentation will give an overview of the current status of RNA therapeutics and particularly cover the medicinal chemistry aspects of sulfur-modified antisense oligonucleotides. We will also discuss the impact of stereochemistry to the drug profile of antisense oligonucleotides in general, present various and orthogonal discovery tactics for the identification of such stereodefined ASOs and particularly focus on the combination of achiral phosphorodithioates with stereodefined phosphorothioate internucleoside linkages. Both, *in vitro* potency and *in vivo* efficacy data will be presented (among others) and a particular focus will be given on drug metabolism. The data package will demonstrate the superiority of such chimeric thioate/dithioate-designs over their stereomixed as well as their fully stereodefined phosphorothioate ASO counterparts and exemplify what an impact medicinal chemistry strategies may have for the further development of RNA therapeutics.

DR CLAUDIA BETSCHART
NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, Basel, Switzerland

Claudia Betschart, Senior Investigator in Global Discovery Chemistry at Novartis Institutes for BioMedical Research.

Claudia Betschart received her PhD in natural sciences from the department of chemistry at the Swiss Federal Institute of Technology (ETH) in Zürich, Switzerland. After postdoctoral studies in Mexico City and at Colorado State University in Fort Collins, she started her carrier as a medicinal chemist end of 1991 with Ciba-Geigy (now Novartis) in Basel, Switzerland. Since then she contributed to drug discovery projects in various disease areas, including neuroscience, bone metabolism, and autoimmunity.

T26

TLR7/8 ANTAGONISTS: FROM SCREENING TO IN VIVO POTENCY

Claudia Betschart (1), Thomas Knoepfel (1), Ralf Glatthar (1), Dirk Behnke (1), Eric Vangrevelinghe (1), Phillip Alper (2), Tobias Junt (1), Stuart Hawtin (1), Pius Loetscher (1), Roland Feifel (1), Michael Faller (1), Jutta Blank (1)

1) Novartis Institutes for Biomedical Research, CH-4002 Basel, Switzerland
2) Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, California 92121, USA

Toll-like receptors (TLRs) are an integral part of the innate immune system. They serve as both extracellular and endosomal sensors for a variety of pathogen-associated molecular patterns. Inappropriate activation of the endosomal receptors TLR7 and TLR8 has been linked to the pathogenesis of autoimmune disorders such as e.g. systemic lupus erythematosus. Antagonists of these receptors are therefore expected to be attractive agents for the treatment of such conditions.

Previous attempts to identify TLR modulators relied on cellular pathway assays, in which TLR expressing cells are stimulated with specific agonists to trigger cytokine release. While this approach has been successfully applied in the past, validation and optimization of hits from cellular screening campaigns can be time and resource intensive. In order to demonstrate target specificity a battery of counter-assays is required and rational optimization is complicated by the complexity of the assay system.

Here we present our efforts to identify and optimize TLR7/8 antagonists starting from an on-target screening campaign. A binding assay suitable for high-throughput screening was established using the endosomal domain of TLR8 and fluorescently labeled probes. The efficient structure based optimization of the inhibition of TLR8 starting from a co-crystal structure of a screening hit will be presented. Encountered limitations in rationalizing the SAR on TLR7 based on structural information gained from TLR8 will also be discussed. The optimization finally resulted in highly potent TLR7/8 antagonists with demonstrated *in vivo* efficacy after oral dosing.

DR KIMBERLY CAMERON

PFIZER, Cambridge, United States

Kimberly Cameron is a Research Fellow in Medicine Design at Pfizer. Kimberly obtained a B.A. at Rutgers University and a Ph.D. in organic chemistry at the University of Colorado in Boulder, where she discovered Lewis acid-promoted annulation reactions working with Prof. Gary A. Molander. Kimberly is a globally recognized drug discovery expert and has led chemistry and interdisciplinary teams targeting diverse biology space including AMPK, ghrelin, prostaglandin receptors and nuclear hormone receptors.

Kimberly's research interests include medicinal chemistry, organic chemistry, kinases, orphan GPCRs, structure-based drug design, and tissue-targeted therapies.

T27

ALLOSTERIC ACTIVATION OF A MASTER METABOLIC REGULATOR AMPK: DRUG DISCOVERY OPPORTUNITIES AND CHALLENGES

Kimberly Cameron

Pfizer Medicine Design, 1 Portland Street, Cambridge, MA 02139, United States

AMPK (5' adenosine monophosphate-activated protein kinase) is a critical metabolic enzyme involved in maintaining whole body and cellular energy homeostasis. AMPK monitors and regulates cellular ATP levels by phosphorylating a multitude of substrates to modulate pathways involved in restoring energy homeostasis. AMPK is a heterotrimeric serine/threonine protein kinase comprised of a catalytic α-subunit in complex with regulatory β and γ-subunits. The presence of multiple gene products for each subunit allows for the assembly of twelve theoretical isoform combinations which differ in expression pattern across tissues and species. Programs at Pfizer have focused on identification of AMPK activators that activate all isoforms as well as selectively activate specific isoforms. Our efforts are focused on the use of AMPK activators for the treatment of key metabolic diseases which were selected based on preclinical and human genetic data. We will highlight strategies used to identify lead matter for these programs, including fragment and virtual screens, along with optimization, biophysical and in vivo characterization. Challenges in the discovery and development of AMPK activators will be described as well as the successful delivery of an isoform selective AMPK activator to the clinic.

NOTES

Oral Communications – Biographies & Abstracts

PROF. PLATO MAGRIOTIS

UNIVERSITY OF PATRAS, Patras, Greece

Since 2006, Plato A. Magriotis, Ph.D. is an Associate Professor of Medicinal Chemistry in the Department of Pharmacy at the University of Patras in Greece and a Research Affiliate with the Department of Chemistry at New York University. Magriotis received his Ph.D. in Chemical Biology with Professor Francis Johnson at Stony Brook University in 1983 and did Postdoctoral work at Harvard University with Nobel Laureate Professor E. J. Corey.

His career started at West Virginia University and continued at Merck & Co. as well as New York University in the U.S., prior to his return to Greece.

Magriotis' research program focuses on the development of new methodology for the synthesis of relevant pharmacophores applied in drug discovery.

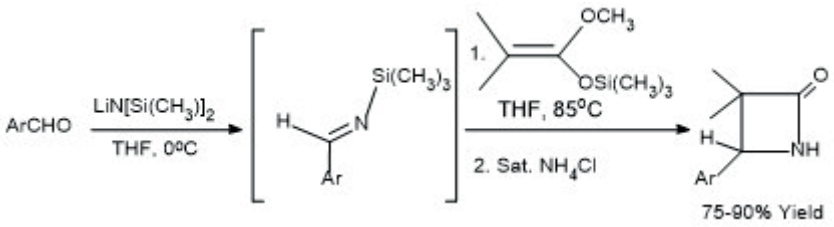
OC01

PRACTICAL AND ASYMMETRIC GILMAN-SPEETER SYNTHESIS OF B-LACTAMS

Adreana Karakoula, Maria Panagioyou, Vasileios Ntemos, Ilia Pitsa, Anastasia Karatza, Chrysoula Kapsokavadi, Plato Magriotis

Laboratory of Medicinal Chemistry, Department of Pharmacy, University of Patras, Greece

A highly efficient synthesis of β-lactams possessing a 4-aryl substituent is described, employing a direct, uncatalyzed Mannich reaction between TMS imines and TMS ketene acetals.The process avoids cryogenic conditions, making it more amenable to process-scale use than related methods. A Gilman-Speeter asymmetric version using an inexpensive catalyst and leading to homochiral unprotected β-lactams is also presented. The latter reaction is applicable to other types of imines such as N-sulfonyl and N-Boc imines.



DR TATJANA BRAUN

SCHRÖDINGER, Mannheim, Germany

Tatjana Braun has studied Bioinformatics at the Technical University and the Ludwig-Maximilian University of Munich. She then obtained her doctorate from the University of Düsseldorf for research mainly focusing on structure modelling using cryo-EM data. In 2017, she joined Schrödinger to work as an Applications Scientist.

OC02

RAPID EXPLORATION OF SYNTHETICALLY TRACTABLE CHEMICAL SPACE AND LEAD OPTIMIZATION USING A COMBINATION OF REACTION-BASED ENUMERATION, ACTIVE LEARNING, AND FREE ENERGY CALCULATIONS

Tatjana Braun (1), Kyle Konze (2), Pieter Bos (2), Markus Dahlgren (2), Karl Leswig (2), Ivan Tubert-Brohman (2), Andrea Bortolato (2), Braxton Robbason (2), Robert Abel (2), Sathesh Bhat (2)

1) Schrödinger GmbH, Q7 23, 68161 Mannheim, Germany
2) Schrödinger Inc, 120 W 45th St, New York, NY 10036, USA

Improving or maintaining the potency of lead compounds, while simultaneously optimizing multiple other properties required for safety and biological efficacy, is a primary objective of lead optimization in small molecule drug discovery.

In this talk we will present a workflow that integrates synthesis-aware compound enumeration, cloud-based free energy calculations, and machine learning approaches for large-scale potency predictions on a time scale that can impact real-world drug discovery projects: Combining *PathFinder* enumeration, *FEP+* binding free energy calculations, and active learning allowed to rapidly optimize R-groups and generate new cores of cyclin-dependent kinase 2 (CDK2) by exploring more than 300 thousand ideas [1]. In this example, the described potency optimization workflow was able to identify 35 ligands with diverse commercially available R-groups and four unique cores with predicted IC50 < 100 nm. Surprisingly, only a small fraction of the profiled corehops had existing matches in the BindingDB, despite featuring typical kinase hinge binding features and being achievable by straightforward synthesis. This indicates that exhaustive mining of easily accessible chemical space is typically not done in drug discovery today, even in a highly explored target class like kinases.

Overall, we expect that the computational techniques of binding free energy calculations, machine learning, synthetically aware compound enumeration, and their huge synergistic effects significantly accelerate the hit-to-lead and lead optimization processes by producing synthetically-tractable potent compounds within a desired property range and rapid turnaround time.

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MR ANGELOS LELIS
UNIVERSITY OF ATHENS, Athens, Greece

Aggelos Lelis obtained his Chemistry degree in 2015 from the National and Kapodistrian University of Athens. He worked in an organic chemistry-related project during his diploma thesis and decided to continue in the area of synthetic medicinal chemistry in a post-graduate level. In 2015 he joined the research group of Prof. Dimitris Georgiadis working in stereoselective synthetic methodologies towards phosphinic peptides, a promising class of Zn-metalloproteases' inhibitors. Currently, he is working towards his PhD thesis in the research group of Prof D. Georgiadis, in collaboration with Dr Efstratios Stratikos from NCSR "Demokritos", with a full scholarship from National Scholarship Institute. His research interests combine the development of novel prodrug technologies applied to phosphinic inhibitors of Zn proteases and the evaluation of stereoselective approaches towards this synthetically underexplored class of compounds.

OC03

A RADICAL APPROACH FOR THE LATE-STAGE FUNCTIONALIZATION OF PHOSPHINIC PEPTIDES

Kostas Voreakos (1), Lelis Angelos (1), Devel Laurent (2), Georgiadis Dimitris (1)

1) University of Athens, Department of Chemistry, Laboratory of Organic Chemistry, Greece
2) Université Paris-Saclay, Institut des Sciences du Vivant Frédéric Joliot, Service d'Ingénierie Moléculaire des Protéines, France

Phosphinic peptides constitute a privileged class of Zn-metalloprotease inhibitors, distinguished by their ability to exhibit enhanced potency and improved selectivity profiles by acting as transition-state analogues [1]. Even though their value as efficient inhibitors of Zn proteases has been widely recognized, cumbersome synthetic routes and lack of attractive "late-stage" diversification strategies are crucial limiting factors for the wide screening of diverse structures during drug discovery. The absence of late-stage functionalization approaches has forced researchers to execute SAR studies by using lengthy and time-consuming synthetic routes in order to achieve some level of diversity at P1 and P1' positions which are the most important determinants of biological activity. Interestingly, the only reliable late-stage diversification methodology existing in the literature (based on 1,3-DCRa affording isoxazole derivatives), was developed 16 years ago and its potential was immediately recognized leading to the discovery of potent and selective inhibitors of several Zn-proteases of medicinal interest [2]. However, the quest of a protocol offering broader diversification possibilities, beyond the isoxazole motif, remained for many years an elusive target.

In this presentation, we present the effectiveness of radical chemistry, and in particular of the Giese-type trapping of alkyl radicals by dehydroalanine phosphinic isosters (DPIs), to the installation of diverse side chains at a late stage of phosphinic pseudopeptides' synthesis. This strategy can be applied efficiently in structures of different levels of complexity, from simple phosphinic pseudodehydroalanine units to dipeptides, building blocks for SPPS or longer peptides. Moreover, requirements for protection of side-chain or backbone termini functional groups are limited to a minimum whereas unprotected phosphinic acid functionalities are fully compatible with the proposed radical addition approach. The possibilities and limitations of tin-free alternatives are also comparatively presented and the complementarity of such approaches is demonstrated. Given the operational simplicity and broad scope, we expect that this methodology will trigger new developments in the discovery of medicinally important phosphinic peptide inhibitors of Zn-dependent enzymes [3].

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EFMC Prize Winner EFMC-YMCS 2018

DR CASSANDRA LEE FLEMING

UNIVERSITY OF GOTHENBURG, Gothenburg, Sweden

Cassandra Fleming obtained her PhD in organic chemistry in 2015 from Deakin University, Australia. Following her doctorate, she joined the group of Prof Joakim Andréasson as a postdoctoral researcher at Chalmers University of Technology, in which her work focused on the development of fluorescent bioactives as molecular tools to probe real-time intracellular events. Cassandra currently works as a Marie Curie postdoctoral fellow at the University of Gothenburg in the group of Prof Morten Grølti.

Her research interests include the development of light responsive molecular tools for the study of disease progression in a cellular setting.

OC04

DEVELOPMENT OF RELEASE-AND-REPORT KINASE INHIBITORS AS MOLECULAR TOOLS FOR INVESTIGATING NEURODEGENERATIVE DISORDERS

Cassandra L. Fleming (1,2), Tord Inghardt (3), Morten Grøtli (1), Joakim Andréasson (2)

1) Department of Chemistry and Molecular Biology, University of Gothenburg, Sweden
2) Department of Chemistry and Chemical Engineering, Chalmers University of Technology, Sweden
3) Cardiovascular, Renal and Metabolism, Innovative Medicines and Early Development, AstraZeneca, Sweden

The aberrant regulation of lymphocyte-specific protein tyrosine kinases (LCK) has been associate with the over activation of microglia cells (important immune effector cells that reside in the central nervous system, CNS) and in turn, the development of Alzheimer's disease (AD).[1] Unfortunately, the detail of LCK's dynamic function and the importance of quantitative, spatial and time-dependent parameters regarding microglia activation are poorly understood. As such, the ability to manipulate LCK activity using light would result in temporal control of enzymatic activity, thus serving as a valuable approach to probe the function of LCK in microglia cells and in turn, further our understanding of AD and related neurodegenerative disorders.

While such studies cannot be performed using conventional LCK inhibitors, we are currently pursuing the development of a stimuli-responsive *release-and-report* system. This is to be achieved through the introduction of a photolabile caging moiety onto a fluorescent LCK inhibitor that exhibits 'OFF-ON' fluorescent changes in concert with the release and subsequent binding of the bioactive to the kinase enzyme. To date, a potent LCK inhibitor that exhibits favourable fluorescent properties for cellular imaging has been developed. The inclusion of an appropriate caging group and its effects on kinase activity is the current focus of the project. In contrast to conventional LCK inhibitors, the development of the photoresponsive kinase inhibitor will allow us to gain spatiotemporal control over LCK activity as well as visualise the decaging process and subcellular localisation of the active kinase inhibitor.

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DR JEAN-BAPTISTE LANGLOIS

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, Basel, Switzerland

Jean-Baptiste Langlois obtained is PhD in organic chemistry from the University of Geneva (Switzerland), where he worked on asymmetric catalysis in the group of Prof. Alexakis. In 2012, he moved to the Massachusetts Institute of Technology (Cambridge, USA) to perform his post-doctoral studies with Prof. Buchwald. Jean-Baptiste came back to Switzerland in 2013 to start his career as medicinal chemist. First, in a startup company named PIQUR Therapeutics focusing on the discovery of new PI3K inhibitors and eventually at the Novartis Institutes for Biomedical Research in Basel. Over the past years, Jean-Baptiste acquired a quite diverse experience, working successively in the fields of autoimmune disorders, oncology and more recently on musculoskeletal diseases.

OC05

STABILIZING INACTIVE CONFORMATIONS OF MALT1 AS AN EFFECTIVE STRATEGY TO INHIBIT ITS PROTEASE ACTIVITY

Jean-Baptiste Langlois (1), Martin Renatus (2), Paul Erbel (2), Nicola Aubin (2), Frederic Bornancin (3), Bertrand Gerrits (2), Christian Wiesmann (2), Jean Quancard (1), Frederic Villard (2), Carole Pissot-Soldermann (1), Achim Schlapbach (1), Carsten Spanka (1), Mickael Sorge (1), Oliver Simic (1), René Beerli (1), Arnaud Decock (2), Riccardo Canova (1)

1) Global Discovery Chemistry, Novartis Institutes for Biomedical Research, Basel, Switzerland
2) Chemical Biology and Therapeutics, Novartis Institutes for Biomedical Research, Basel, Switzerland
3) Autoimmunity, Transplantation and Inflammation, Novartis Institutes for Biomedical Research, Basel, Switzerland

The paracaspase MALT1 (mucosa associated lymphoid tissue lymphoma translocation protein 1) plays an important role in various immune pathways and has been proposed as a therapeutic target for auto-immune disorders as well as cancers (i.e. DLBCL). We explored different mechanisms to inhibit the protease activity of MALT1 and discovered two unrelated chemical scaffolds. Biophysical and structural studies revealed that both scaffolds stabilize the protease in an inactive conformation. While one ligand binds to the allosteric site at the interface between the caspase and the IG3 domain, the other ligand binds to the active site in a so far undescribed mechanism. Iterative structure based drug discovery on one scaffold resulted in the identification of a potent, selective and bioavailable MALT1 inhibitor.

DR STEPHANIE GUERET

ASTRAZENECA-MPI SATELLITE UNIT, Dortmund, Germany

After studying organic chemistry at the University Claude Bernard Lyon 1, France, Stéphanie Guéret completed her PhD in 2011 from the University of Auckland, New Zealand where she achieved the total synthesis of the spiroimine unit of the Spirolide family of natural products. She then joined the Novartis Institute for Biomedical Research (NIBR) in Basel, Switzerland as a presidential postdoctoral fellow and developed a new class of cyclic peptidomimetics.

In 2015 she took a senior research scientist position at AstraZeneca to join the AstraZeneca-Max Planck Institute Satellite Unit, embedded in the group of Prof. Waldmann in Dortmund, Germany. Together with a small team of students and scientists, she has led major projects of the satellite unit focusing on the synthesis development of mixed macrocycles to modulate protein-protein interactions and the use of “new modalities” such as stabilized peptides to address challenging targets.

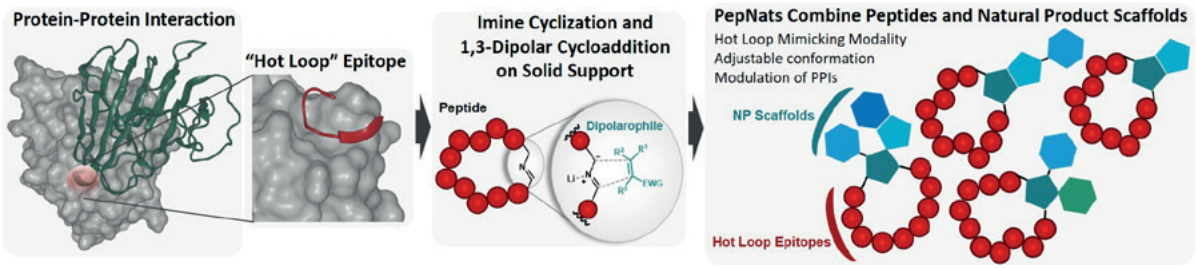
Her current research interest is synthetic and medicinal chemistry with broadening towards chemical biology to solve key questions on how to move forward novel chemical modalities towards drug-like compounds.

OC06

MACROCYCLIC MODALITIES FOR MODULATION OF PROTEIN-PROTEIN INTERACTIONS

Stéphanie Guéret (1,2)

1) AstraZeneca-Max Planck Institute Satellite Unit, Dortmund, Germany
2) Medicinal Chemistry, Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden



Hoot loops, composed of peptide sequences with their C- and N-terminus in spacial proximity, have been identified as frequently occurring structural protein motifs which contribute crucially to protein-protein interactions (PPIs). Macrocyclic peptides have been explored to inhibit PPI mediated by hot loops. However, peptide macrocyclization is currently restricted to classical methods such as lactam, disulfide, olefin, triazole and simple aromatic bridges. Moreover, their lengthy synthetic routes and lack of conformational tuning limit their diversity, availability and efficient adjustment of the peptide epitope conformation.

Herein, we report de novo combination of peptide sequences from hot loops and natural product (NP)-inspired structures to afford macrocyclic Peptide-Natural Product modalities (PepNats) to modulate PPIs.[1] Efficient access to PepNats is obtained via intramolecular imine cyclization followed by a late stage diastereoselective cycloaddition on solid support. Rapid structural variation of both the Csp3 moiety and the peptidic unit is enabled by leveraging the power of solid phase synthesis in combination with stereoselective synthesis of a NP-like scaffold. These macrocyclic modalities adopt a preferred conformation in solution as revealed by NMR and conformational analysis. Further, we provide proof of principle by the design, synthesis and analysis of two macrocyclic PepNat collections using the DINNN and RFF peptide loop epitopes from the inducible nitric oxide synthase (iNOS) and human agouti-related protein (AGRP) respectively. The PepNats derived from the iNOS hot loop are nanomolar binders of the SPSB2 adaptor protein in the E3 ubiquitin ligase complex. Flexible modification of the NP unit in the RFF containing PepNats gives modulable selectivity profile for the different melanocortin receptor sub-types. Taken together, the unprecedented combination of NP scaffolds with a hot loop on solid support enables the rapid identification of novel hot loop mimics with conformationally constrained and biologically relevant structure.

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DR LENI RITMALENI
GADJAH MADA UNIVERSITY, Yogyakarta, Indonesia

Dr Ritmaleni received her PhD from the School of Chemistry, University of Bristol, United Kingdom in 2004, under supervision of Prof. V. K. Aggarwal. She was as a visiting scholar at Department of Chemistry, Graduate School of Science, Tohoku University, Japan in 2013 and visiting scientist at School of Pharmacy, University of Groningen, The Netherland in 2014. Now, she is appointed as a Director of Curcumin Research Center, Faculty of Pharmacy, Gadjah Mada University apart as Associate Professor at Faculty of Pharmacy, Gadjah mada University. She is a recipient of Elsevier Foundation Award 2014 in Chemistry, Study UK Alumni 2017 and ASEAN Science Leadership Program Fellow. She is a reviewer of Journal of Molecular Structure, Elsevier and reviewer of Chemistry Select, Wiley-VCH.

Her research interest is focused on the synthesis of active molecule as drug candidate especially curcumin analogs. She has collaboration with Prof. Tasuki Kaneko from TB Alliance, USA where she got funding for her research on antituberculosis activity of curcumin analog compounds. She also has collaboration with Prof. Herman Spaink from Leiden University, The Netherlands for in vitro/in vivo assay of antituberculosis activity of curcumin analogs by using Zebra Fish as a model.

OC07

ANTIMICROBIAL ACTIVITY OF CURCUMIN ANALOG PGV-6, HGV-6 AND GVT-6

Ritmaleni Ritmaleni (1,2), Sardjiman Sardjiman (1,2), Indah Purwantini (3)

1) Curcumin Research Center, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia
2) Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia
3) Deaprtment of Biological Pharmacy, Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia

PGV-6, HGV-6 and GVT-6 are three of curcumin analog that synthesized in Faculty of Pharmacy, Gadjah Mada University, Indonesia.[1,2] This research is aimed to screen the antimicrobial activity of those three compounds by using micro-dilution method.Synthesis of PGV-6, HGV-6 and GVT-6 are carried out by using the aldol condensation reaction between a keton (cycopentanone, cyclohexanone, acetone) and aromatic aldehyde (3,5-Dichloro-4-hydroxybenzaldehyde) in acid condition. First work was to see the inhibition percentage and the second experiment is to see the lowest sensitivity against microbes (bacteria and fungi), of three compounds by using micro-dilution method. From the results, it was obtained that the antimicrobial test against seven bacteria and one fungi showed that PGV-6 only inhibits the growth of *Staphylococcus aureus* bacteria; HGV-6 inhibits *Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacteria; GVT-6 inhibits the growth of *Klebsiella pneumonia*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus faecalis* bacteria. None is active against *Candida albicans* fungi. GVT-6 is still sensitive against bacteria at 250 mL/mg of the concentration. GVT-6 is promising to be more developed as antimicrobial agents

Keywords: PGV-6, HGV-6, GVT-6, antimicrobial, bacteria, fungi

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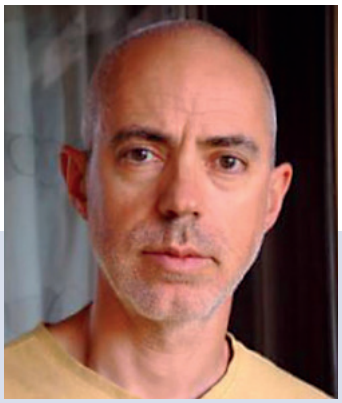

DR JOSE IGNACIO MARTIN

GSK, Tres Cantos, Spain

Born in Salamanca, he completed his studies at the University of Salamanca. He then joined Dr S. Arseniyadis' group at the Institut de Chimie des Substances Naturelles (ICSN-CNRS, France) for a first 3-year postdoctoral stage where he was involved in the total synthesis of taxoids and Lead tetraacetate mediated one-pot multistage transformations on unsaturated 1,2-diols. In 2000 he moved to USA and joined Prof. A. S. Kende group at the University of Rochester (NY) to deal with the first total synthesis of the alkaloids Stemonamide and Isostemonamide. In January 2002, he started working at Merck & Co as Senior Research Chemist in its Istituto di Ricerca di Biologia Moleculare at Pomezia (Italy) where he spent almost eight years working in hepatitis C and cancer. In November 2008 he returned to Spain to work at the Spanish National Cancer Centre (CNIO) for 3 years. Since 2012 he works at GSK in the Diseases for Developing World unit in the Malaria unit.

OC08

DISCOVERY OF GSK701, A NOVEL ORALLY EFFECTIVE PRECLINICAL DRUG CANDIDATE FOR THE TREATMENT OF MALARIA

Jose Ignacio Martin-Hernando

GSK. Severo Ochoa 2, 28760 Tres Cantos, Madrid, Spain

Last year 2018 was an inflection point in our global Malaria fight. After several years of improvement, progress has stalled. An estimated 219 millions cases and 435000 related deaths were reported in 2017[1] that although are a slight improvement in number of deaths does not translate in a statistically significant advance against Malaria.

On top of that, the emerging resistance to current front-line ACTs (Artemisinin Combination Therapies) detected in endemic countries is adding additional pressure to the antimalarial community.

During the past few years, the antimalarial community has focused their efforts on phenotypic screening as a pragmatic approach to identify new hits. Within the TCAM[2] set of phenotypic hits identified at GSK, a pyrrolidinamide chemical series was selected because its chemical novelty and putative new MoA, offering promising properties as antimalarial.

Lead optimization efforts within the pyrrolidinamide series led to the identification of GSK701 as a new preclinical candidate that will offer opportunities linked to its killing profile and potency comparable to artemisinins as well as its new mode of action. The overall properties of GSK701, including the low predicted human dose, constitute a promising profile supporting further development to provide novel antimalarial therapeutic opportunities.

A detailed description of the Medicinal Chemistry identification and development of GSK701 will be provided in this comunication.

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

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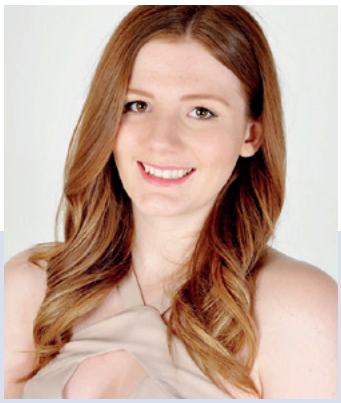


MS LOUISE EAGLING
UNIVERSITY OF BRISTOL, Bristol, United Kingdom

Louise Eagling obtained her MChem degree in 2015 from the University of East Anglia. As part of her degree, she undertook an industrial placement working for Novartis as a medicinal chemist. Her final year project was carried out under the supervision of Dr. Paz Muñoz-Herranz, in collaboration with Novartis, exploring the platinum catalysed inter- and intramolecular addition of nucleophiles to allenes to obtain multi-heteroaromatic structures with potential biological activity. She is currently working towards her PhD at the University of Bristol under the supervision of Prof. Jonathan Clayden as part of the Chemical Synthesis CDT with CASE sponsorship from Syngenta. Her PhD has focussed on the total synthesis of Arogenate and derivatives with potential agrochemical or medicinal applications.

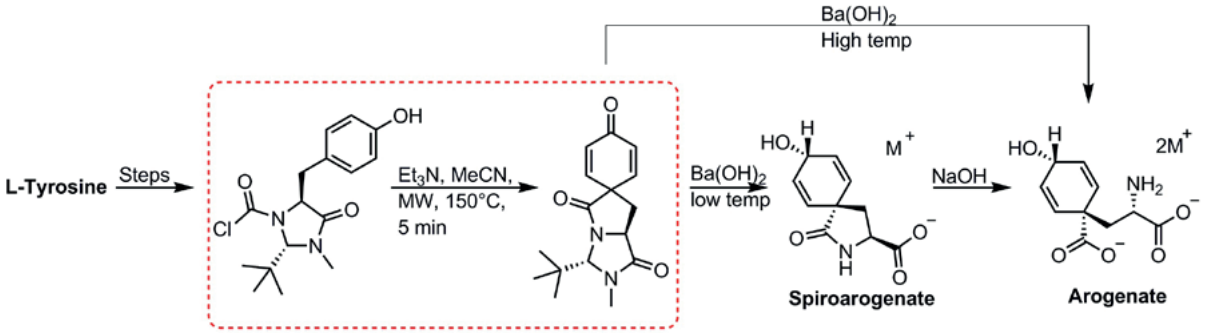
OC09

DEVELOPING A 'REVERSE-BIOMIMETIC' SYNTHESIS OF AROGENATE AND ITS ANALOGUES

Louise Eagling (1), Daniel Leonard (1), Iñaki Urruzuno (1), John Ward (1), Steve Wailes (2), Jonathan Clayden (1)

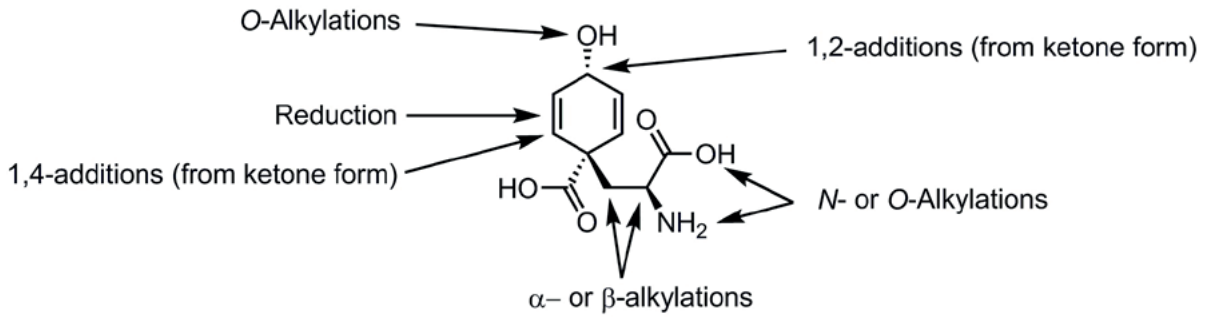
1) University of Bristol, School of Chemistry, Cantock's Close, Bristol, BS8 1TS, United Kingdom
2) Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, United Kingdom

Arogenate is a key intermediate in the shikimate biosynthetic pathway to aromatic amino acids tyrosine and phenylalanine. Only two syntheses of arogenate have been reported, neither of which exploit the obvious starting material, L-tyrosine itself.[1],[2] Uniquely, our work focuses on a 'reverse-biomimetic' synthesis of arogenate starting from this inexpensive, enantiopure amino acid. Interestingly, the synthetic route proceeds via a novel and mechanistically unusual dearomatising spirocyclisation reaction. This intramolecular acylation, which utilises a carbamoyl chloride tether to produce a spirocyclic lactam, can be performed using low-cost reagents and without the need for heavy metals or toxic species.



Scheme 1: Overview of the synthetic concept.

The biosynthetic pathways to aromatic amino acids are present in plants, bacteria and fungi but completely absent in animals.[3] Targeting the enzymes involved in this pathway with synthetic analogues of arogenate could enable the development of new, safe and selective herbicides and antibiotics. Particular interest lies in compounds which demonstrate increased stability or an inability to rearomatize, as these may confer desirable inhibitory activity.



Scheme 2: Derivatisation of arogenate for inhibitory activity studies.

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EFMC Prize for a Young Medicinal Chemist in Academia

DR ANDREAS KOEBERLE

UNIVERSITY OF JENA, Jena, Germany

Andreas Koeberle is research group leader and lecturer at the University of Jena (Germany). He graduated in biochemistry and received a Ph.D. in Medicinal Chemistry/Analytics at the University of Tuebingen (Germany) in 2009. After postdoctoral studies at the University of Tokyo (Japan), he joined the Chair of Medicinal/Pharmaceutical Chemistry at the University of Jena (Prof. Oliver Werz), where he established the institutional lipidomics facility. In 2018, he became visiting professor at the University of Vienna (Austria). Offers for full professorships followed in 2017 from the Paracelsus Medical University (Salzburg, Austria) and 2019 from the University of Innsbruck (Austria). His research focuses on the characterization of lipid signaling pathways at the interface of inflammation, cancer and homeostasis and on the identification of drug targets and leads with focus on natural products. Detailed information: https://www.pharmazie.uni-jena.de/Abteilungen.html

OC10

FROM THE ELUCIDATION OF THE MECHANISM OF VITAMIN E TO THE DESIGN OF INNOVATIVE DRUGS THAT LIMIT INFLAMMATION AND ENHANCE RESOLUTION

Andreas Koeberle

Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Friedrich-Schiller-University Jena, Philosophenweg 14, 07743 Jena, Germany

Major advances in drug development are often inspired by nature, which provides a high diversity of evolutionally optimized scaffolds [1]. Progress is, however, hampered by the metabolism of natural products in gut and liver, and the failure of *in vitro* screening to identify bioactive metabolites that are produced in this process. To solve this problem, we quantitatively analyzed natural product metabolites in humans, rodents and organoids by targeted mass spectrometry prior to semi-synthesis and biological evaluation of metabolite series, with target identification being supported by lipidomic profiling [2].

In a proof-of-concept study, we investigated whether bioactive metabolites mediate the immune functions of vitamin E. While the essential fat-soluble vitamin has long been viewed as a mere antioxidant, non-redox mechanisms have recently moved into research focus, and oxygenized metabolites have been proposed as signaling molecules [3]. From a library of metabolites with potential physiological relevance in humans, we identified an endogenous vitamin E metabolite that limits inflammation and revolutionizes our current understanding of the molecular mechanisms of vitamin E [4]. This metabolite suppresses the biosynthesis of pro-inflammatory leukotrienes at sites of inflammation by targeting 5-lipoxygenase through a unique allosteric mechanism while increasing the systemic concentrations of lipid mediators that resolve inflammation. Structural optimization of vitamin E metabolites yielded orally active derivatives with favorable efficacy and selectivity in human leukocytes [5] and in experimental models of peritonitis, dermatitis, and asthma.

By unraveling the mechanism of vitamin E, we designed bioinspired drug candidates that might overcome adverse effects of current anti-inflammatory drugs on resolution and regeneration.

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EFMC Prize for a Young Medicinal Chemist in Industry

DR RADKA SNAJDROVA

NOVARTIS INSTITUTE OF BIOMEDICAL RESEARCH, Basel, Switzerland

Radka obtained her PhD from Vienna University of Technology in 2007 where she worked on the asymmetric synthesis of lactones using a combination of chemical and biocatalytic approaches. She received an Erwin-Schroedinger Fellowship and spent 1 year of postdoctoral study at York University in the UK, exploring the development of novel biocatalysts for organosilane chemistry. In 2009, Radka moved to University of Greifswald, Germany as a senior postdoctoral fellow to develop a high-throughput screening approach for in vivo selection and cell sorting, with the primary goal of identifying novel enantioselective enzymes.

In 2011, she transitioned to industry with a one year role at a lab focused on supporting chemists at GSK to take advantage of biocatalytic technologies (Novacta), prior to directly joining Chemical Process Development at GSK, UK as Project leader responsible for the development and implementation of new biocatalytic technology in both pre- and post-commercialisation routes. Since Dec 2016, Radka is leading the Bioreactions group in Global Discovery Chemistry at Novartis Institute for Biomedical Research in Basel.

OC11

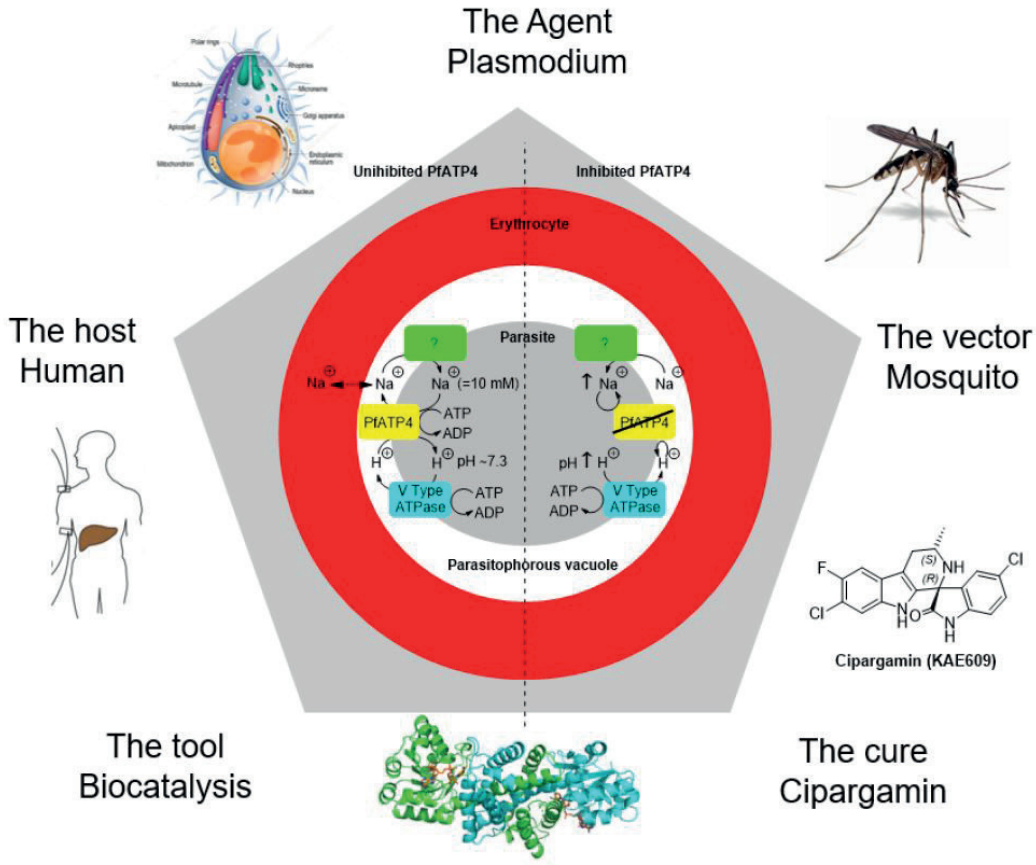
CIPARGAMIN-BIOCATALYSIS IN THE DISCOVERY AND DEVELOPMENT OF AN ANTIMALARIAL DRUG

Radka Snajdrova (1), Thomas Ruch (2), Elina Siirola (1)

1) Global Discovery Chemistry, Novartis Institute of Biomedical Research (NIBR), Novartis Pharma AG, Lichtstrasse, CH-4056 Basel, Switzerland
2) Chemical and Analytical Development (CHAD), Technical Research and Development (TRD), Global Drug Development (GDD), Novartis Pharma AG, Lichtstrasse, CH-4056 Basel, Switzerland

Biocatalysis has gained tremendous relevance in pharmaceutical industry over last decade. It has proven its utility in delivering green, atom efficient and economically viable routes, as well as frequently facilitating routes, inaccessible to traditional synthetic chemistry, towards drug candidates and APIs. It is considered as one of the top priority technologies for drug substance manufacturing at Novartis and is applied to the synthesis of APIs at all stages across the drug development cycle.

This talk covers several aspects of biocatalysis in discovery and in development of the anti-malaria drug Cipergamin (KAE609), including the importance of enzyme discovery and engineering.



DR MIRIAM O'DUILL

NATIONAL UNIVERSITY OF IRELAND, Galway, Ireland

Miriam O'Duill obtained her MChem from the University of Oxford (Merton college) in 2011. In 2015, she completed her PhD at the same university under the supervision of Véronique Gouverneur, developing late-stage fluorination and perfluoroalkylation methodology with a view towards the radiolabelling of new PET tracers. After a two-year stint as a DAAD Postdoctoral Fellow with Keary M. Engle at the Scripps Research Institute in La Jolla, California, investigating transition-metal catalysed alkene functionalisation, Miriam joined the School of Chemistry at the National University of Ireland, Galway as a lecturer in January 2018.

OC12

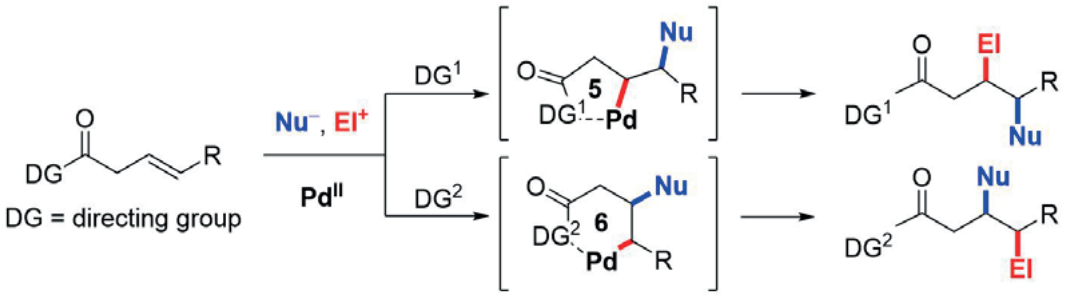
REMOVABLE DIRECTING GROUPS FOR LATE-STAGE FUNCTIONALISATION

Miriam O'Duill (1), Arann Drohan (1), Keary M. Engle (2)

1) National University of Ireland Galway, School of Chemistry, University Road, Galway, H91 TK33, Ireland
2) The Scripps Research Institute, Department of Chemistry, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA

Directing groups have become pivotal in controlling the stereo- and regiochemistry of transition metal catalysed C–H activation and olefin difunctionalisation reactions.[1] Directed transition-metal-catalysed approaches offer powerful strategies for the late-stage functionalisation of molecules, which is of particular interest in the development of lead compounds in medicinal chemistry programmes without the need for costly *de novo* syntheses of each target.[2]

Regiocontrol in these reactions is generally achieved through formation of a stable, five-membered palladacycle intermediate. However, recent work in the Engle lab has demonstrated that the less stable 6-membered palladacycles can be accessed in Pd(II) catalysed alkene functionalisation through the use of pincer-like tridentate directing groups that suppress competing β-hydride elimination, enabling regiodivergent functionalisation strategies based on the choice of directing group (Scheme 1).[3]



Scheme 1 Directing-group-controlled regioselectivity in palladium-catalysed alkene functionalisation

While most of these directing groups are reusable,[4] their removal often requires harsh conditions which limits their functional group compatibility and synthetic utility – especially in industrial applications. An important area of research is thus the development of new families of directing groups that show the same level of reactivity and selectivity of those currently employed, combined with a mild removal strategy.[5]

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NOTES

Poster Communications

FLUORESCENT OLIGONUCLEOTIDE PROBES FOR DETECTION OF BREAST CANCER MARKER

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Diagnosis and treatment of breast cancer can be greatly enhanced and personalized based on the quantitative detection of mRNA markers. Here, we targeted the development of a fluorescent oligonucleotide probe to detect specifically the HER-2 mRNA breast cancer marker.[1] We have selected the chromophore of the Green Fluorescent Protein (GFP), 4-hydroxybenzylidene imidazolinone (HBI), as a fluorophore covalently bound to an oligonucleotide probe and potentially capable of intercalating within a probe-RNA duplex. We first synthesized the two-ring scaffold of the HBI chromophore and coupled it to 2'-deoxyuridine at C5-position via a 7-atom-spacer, to give **1**. Indeed, in the highly viscous glycerol used to mimic the reduced conformational flexibility of the intercalated HBI, chromophore **1** displayed a quantum yield of 0.29 and brightness of 20600 $M^{-1}cm^{-1}$, while no fluorescent signal was observed in methanol. Next, we synthesized a 20-mer oligonucleotide probe incorporating **1** at position 6 (5'-CCCGTUTCAACAGGAGTTTC-3'), ON^{HBI}, (**ON1**) targeting nucleotides 1233–1253 of HER-2 mRNA, **(ON2)**. A 16-fold enhancement of (**ON1**) emission intensity upon hybridization with the complementary RNA **(ON2)** vs that of the non complimentary oligonucleotide probe (**ON4**) indicated the presence of the target oligonucleotide (quantum yield 0.52; brightness 23500 $M^{-1}cm^{-1}$). The intercalative binding mode of the HBI fluorophore was demonstrated by circular dichroism. Furthermore, an 11-fold enhancement of **(ON1)** emission (quantum yield 0.50; brightness 23200 $M^{-1}cm^{-1}$) was observed when the probe was mixed with total RNA extract from a human cell line that has high levels of HER2 mRNA expression. Thus, we propose ON^{HBI} as a promising probe potentially useful for the sensitive and specific detection of HER2 mRNA breast cancer marker.

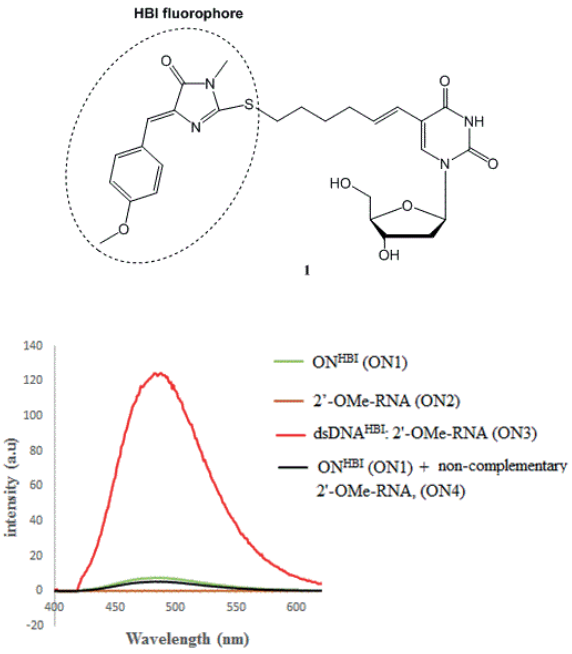

Fig. 1. Emission spectra of ON^{HBI} **(ON1)**, 2'-OMe-RNA **(ON2)**, $dsON^{HBI}$: 2'-OMe-RNA, **(ON3)** and $dsON^{HBI}$:non-complementary 2'-OMe-RNA **(ON4)** (0.2 μM) measured in PBS buffer (pH 7.4, 25 °C), λ_{ex} 390 nm.

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DESIGN AND SYNTHESIS OF NEW OXADIAZOLONE DERIVATIVES AS POTENTIAL ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE (sGC)

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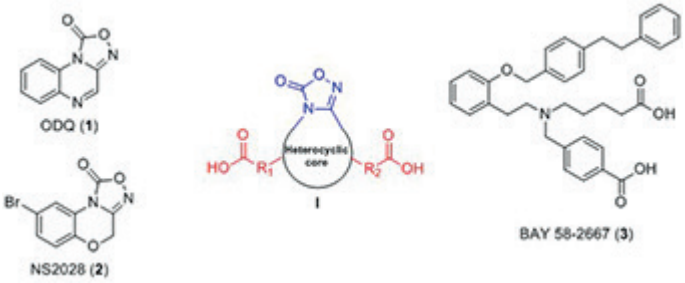
Soluble guanylyl cyclase (sGC) is the main endogenous signaling "receptor" of NO and constitutes a proven, attractive therapeutic target for the treatment of cardiovasular diseases. sGC is a heterodimeric protein composed of one alpha (α_1 or α_2) and one beta (β_1 or β_2) subunit, with a prosthetic heme group located in the H-NOX domain of the β-subunit. Activation of sGC is accomplished by endogenous or donor-derived nitric oxide (NO) binding to ferrous (Fe^{+2}) heme moiety. Reduced bioavailability of NO, removal of the prosthetic heme group or its oxidation to the ferric (Fe^{+3}) state leads to sGC activity impairment seen in various pathological states.[1]

Removal of the heme moiety or its oxidation is achieved by using the synthetic compounds ODQ (**1**) and NS2028 (**2**), leading to impairment of sGC activity.[2] In contrast, the compound BAY 58-2667 (**3**) has been characterized as a NO- and heme-independent activator of sGC.[3] Notably, the activation of sGC by BAY 58-2667 is more potent after removal or oxidation of the heme moiety. Based on activity and binding assays as well as spectroscopic studies, it is assumed that BAY 58-2667 is able to occupy the spatial structure of the sGC porphyrin ligand.[4]



In the present study, we designed and synthesized novel molecules **I** which combine crucial structural features of compounds **1–3**. In particular, they bear both an oxadiazolone ring similar to the sGC inhibitors **1**, **2** and carry substituents with carboxylic groups similar to the sGC activator **3**. We assumed that the oxadiazolone ring would contribute to the oxidation of sGC heme group, enabling the binding of the molecule in the cavity of the H-NOX domain of sGC. Furthermore, we hypothesize that the incorporated carboxylic substituents could mimic the propionic side chains of the heme, thus enabling the formation of hydrogen bond interactions with crucial amino acid residues of the H-NOX domain.

Our endeavors towards the synthesis of the target compounds **I** will be presented. Furthermore, the effective oxidation and replacement of the heme prosthetic group of HNOX domain from *Nostoc sp*. will be tested using the ^{15}N-labelled recombinant HNOX using UV-vis spectroscopy and high-resolution NMR spectroscopy through ^{1}H-^{15}N HSQC experiments according to established experimental protocols.

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TOWARDS THE TOTAL SYNTHESIS OF MYCAPOLYOL A

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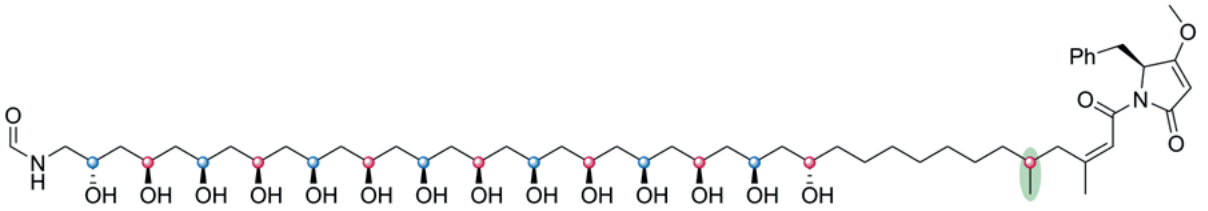
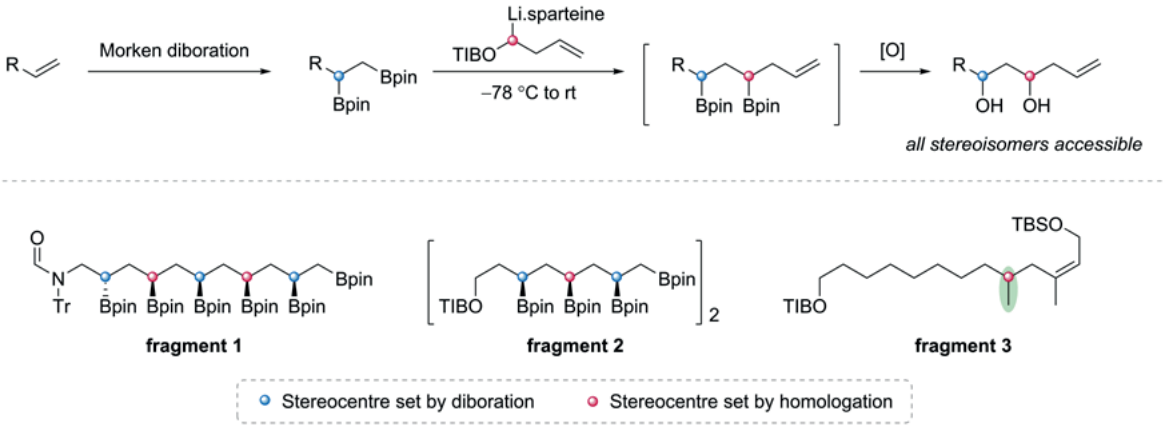


Mycapolyol A

Mycapolyols A-F are 6 unusual PKS metabolites which exhibit cytotoxicity against HeLa cells, isolated by Fusetani and co-workers from the marine sponge *Mycale izuensis* in 2005.[1] There are no reported syntheses of any mycapolyols in the literature to date.

The key synthetic challenge in mycapolyol A is the extended 1,3-polyol unit, comprising 14 stereodefined contiguous but skipped hydroxyl groups. Previous work in the Aggarwal group demonstrated the stereocontrolled synthesis of secondary-secondary and secondary-tertiary 1,3-diols by performing lithiation–borylation reactions with 1,2-bis(boronic esters),[2] which can be obtained through asymmetric diboration of terminal alkenes.[3] Iterative enantioselective alkene diboration and reagent-controlled homologation with a homoallylic benzoate would enable the construction of a stereodefined 1,3-polyol. No repetitive oxidation level changes or functional group interconversions are necessary between iterations, since the boronic esters both mask the hydroxyl functionality, which can be revealed in a later stereospecific oxidation, and enable the homologation through lithiation–borylation reactions.



Retrosynthetic analysis of mycapolyol A suggested a modular approach; fragments 1, 2 and 3 will be prepared separately then coupled together. The optimized synthesis of the 3 key fragments and their combination through lithiation–borylation reactions will be presented, along with model studies for the endgame steps. In addition, fragment 3 contains the one undefined stereocentre at C-5 in mycapolyol A (highlighted); its configuration can be set unambiguously through the choice of either enantiomer of α-stannyl ethyl benzoate for the homologation and so this stereocentre has now been assigned through synthesis.

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NOVEL NANOBIOHYBRID COMPOUNDS TO SUPPRESS THE GROWTH OF SUPERBURGS

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Abstract. A new approach, based on the latest achievements of nanotechnology, medical chemistry and molecular biology is proposed to obtain prodrugs suppressing the growth of bacteria resistant to a wide spectrum of antibiotics.

The discovery and introduction of antibiotics is among the most important achievements of the 20th century. Their wide application in medical practice made it possible to significantly alleviate the course of illnesses and reduce mortality from infectious diseases. However, nowadays practically all pathogenic bacteria and viruses have developed resistance to most clinically important medicinal preparations, hence, there is a need in new drugs acting on new targets and being active against resistant strains of pathogens.

Recently we have synthesized 2'-deoxypyrimidine nucleoside derivatives bearing extended alkyloxymethyl or alkyl(1,2,3-triazol-1-yl)methyl substituents at C-5 position and demonstrated their effective bacteriostatic activity against two Mycobacterium tuberculosis strains [1] as well as against a set of Gram-positive bacteria [2]. However, the nucleosides with large hydrophobic fragments are insoluble in water, thus, limiting the biological investigations.
Herein we present a new approach for transporting medicinal agents into bacterial cells to their targets, namely, the preparation of conjugates of biologically active nucleosides with nanoparticles.
To solve this problem a linker group was introduced coupling a nucleoside moiety with significant antibacterial activity to a nanoparticle,. We have shown that the hydrolysis half-life time of this type of compounds in human blood serum with the release of the original nucleoside was 6-10 hours, which is optimal for prodrugs. We have developed fundamentally new nanostructures with uniquely high optical properties (narrow fluorescence peak, high extinction, high efficiency of two-photon excitation) and offered an efficient method for obtaining conjugates [nucleoside-nanoparticle].
The results of the interaction of conjugates [nucleoside-nanoparticle] with bacteria will be discussed.

ACKNOWLEDGMENT The work was supported by the Russian Foundation for Basic Research, grant 17-00-00395 KOMFI.

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SYNTHESIS, CHARACTERIZATION, ANTICANCER ACTIVITY AND MOLECULAR DOCKING OF SOME NEW SUGAR HYDRAZONE AND ARYLIDENE DERIVATIVES

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New sugar hydrazone moieties and their oxadiazoline derivatives and arylidene analogues were prepared. The prepared compounds were chemically elucidated by spectroscopic analysis such as nuclear magnetic resonance for hydrogen 1HNMR and carbon 13CNMR, elemental analysis and Infrared (IR), and then the prepared compounds were allowed to purify and tested against breast cancer. Compounds 4c, 4d, 6b and 6d exhibit very high to moderate anti-breast cancer activity (MCF-7) of inhibitory percentage 96.19, 93.08, 74.33 and 86.05 % while the reference 5-Fluro Uracil give inhibitory percentage 96.02 %.

Keywords: Sugar hydrazones, arylidene derivatives, oxadiazolines, molecular docking, antimicrobial activity.

A PALLADIUM-CATALYZED DOMINO REACTION TO ACCESS 3-AMINO-2H INDAZOLES FROM HYDRAZINES AND 2-HALOBENZONITRILES

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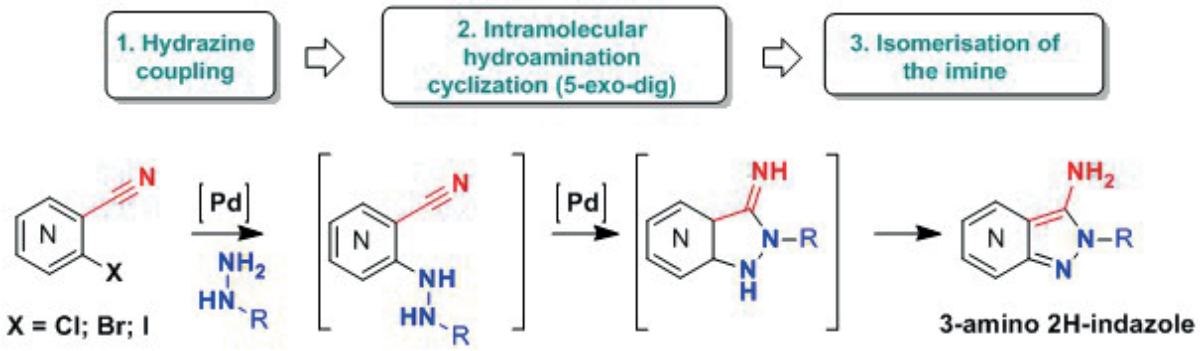
Heterocyclic compounds have proven to be very effective frameworks for the development of drugs and recently the indazole scaffold has gained increasing attention for its application in drug discovery. They have been shown to interact with a variety of targets, especially kinases, as documented by the growing number of reports of biologically active indazole derivatives. Indazoles have also been employed as isosteres for other privileged structures such as indoles, benzimidazoles and benzothiazoles among other and they have been shown to interact with a wide variety of targets. Consequently, there is a great potential of indazoles as druggable frameworks but the important direct regioselective access to the N-substituted 2H-indazoles continues to be a challenging task with only a limited number of available methods.



We have developed a novel palladium-catalyzed domino reaction for the selective synthesis of 3-amino-2H indazoles by using readily available 2-halobenzonitriles and hydrazines as building blocks for this rarely described framework. For this purpose, we built upon previous results from our lab regarding a straightforward domino reaction sequence, consisting of a regioselective palladium catalyzed coupling of mono-substituted hydrazines with 2-halobenzonitriles, followed by an intramolecular hydroamination through a 5-exo-dig cyclization to afford the aromatic 3-amino-2H-indazole analogues in good to excellent yields.

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NOVEL AND SELECTIVE INHIBITORS OF TRIOSEPHOSPHATE ISOMERASE FROM LIVER FLUKE WITH ANTI-TREMATODE ACTIVITY

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Trematode infections such as schistosomiasis and fascioliasis have emerged as important tropical infections. An estimated 250 million people worldwide suffer these infections and agricultural losses caused are estimated at more than US$ 6 billion per year.[1] The actual treatments for these infections are few, old, non-effective, with toxicity issues and a high resistance ratio.[2] Triosephosphate isomerase (*Fh*TIM), an enzyme of the glycolytic pathway emerged as a useful drug target to many parasites including *Fasciola hepatica*.[3] Here, we report the first crystal structure of this enzyme at 1.9 Å resolution. We screened the recombinant protein produced in *Escherichia coli* against an in-house chemical library containing 340 small compounds belonging to different chemotypes.[4] We found 21 compounds that selectively inhibit this enzyme, which are the first reported. We explored the interaction between target and compounds by Microscale Thermophoresis Studies and identified a potent interaction between compound LIDENSA187 and *Fh*TIM, which showed an IC_{50} of 5 µM and a K_d of 66 nM. In only 4 hours it killed the juvenile form with an IC_{50} of 3µM, better than *in vitro* triclabendazole (TCZ) activity, which takes 24 hours and 10 times higher doses to kill the parasites. Interestingly, we discovered *in vitro* inhibition of *Fh*TIM by TCZ, with an IC_{50} of 7 µM suggesting a previously uncharacterized role of FhTIM in the mechanism of action of this drug. Compound LIDENSA187 was also active against *Schistosoma mansoni* in both juvenile and adult forms. We compared the compound's selectivity with rabbit and human enzyme homologues and assessed the toxicity *in vitro* in different cell types and acute toxicity in mice. In conclusion, we describe a promising drug candidate to control neglected trematode infections of human and animal health.

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ANTIBACTERIAL AND ANTITUMORAL ACTIVITY OF CYCLAM DERIVATIVES

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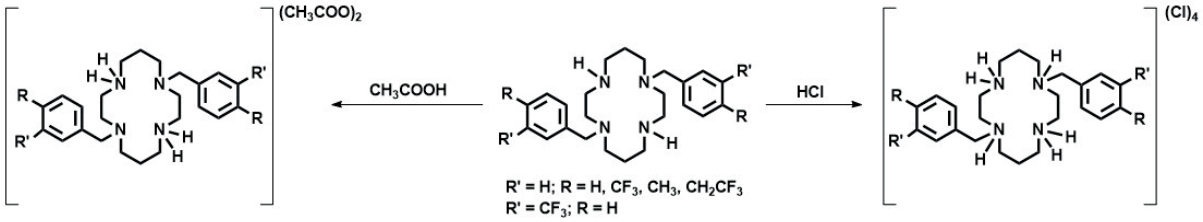
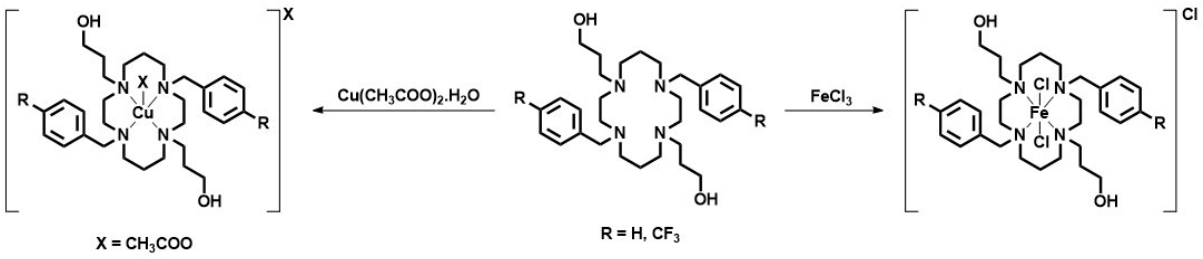
Cyclams are macrocyclic polyamines which medical interest was fueled by the therapeutic potential of a bicyclam derivative in HIV infection, inflammatory diseases, cancer and stem-cell mobilization.[1] Taking advantage of the biocompatibility, the high metal chelation stability constants and the possibility of N-functionalization of the cyclam backbone, a variety of compounds have been explored in a wide range of medicinal applications.[2] The use of cyclams and cyclam-based complexes as antimicrobial and antitumoral agents has been described in recent years. In particular, *trans*-disubstituted cyclam salts (see Scheme 1) revealed to be active antibacterial agents against both Gram-positive and Gram-negative bacteria.[3]



Scheme 1

In the field of anticancer applications, several attempts are being made, mostly with Cu^{II} complexes, envisaging their use as $^{64/67}Cu$ radionuclides.[4] Recently, we found that *trans*-disubstituted cyclam derivatives and their Cu^{II} and Fe^{III} complexes (see Scheme 2) display relevant antitumoral activity against HeLa cancer cell lines.[5] Results on both antibacterial and antitumoral activity of cyclam derivatives will be presented and discussed. To the best of our knowledge, this is the first report on an iron-cyclam compound tested as anticancer agent.



Scheme 2

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STUDY ON THE MAO-B INHIBITION BY NEW N,N'-DISUBSTITUTED BENZIMIDAZOLE HYDRAZONES

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Monoamine oxidase-B (MAO-B) is an enzyme involved in the neurodegenerative process associated with aging, and also involved in neurodegenerative diseases including Parkinson's and Alzheimer's disease [1]. The neuroprotective drugs and the selective monoamine oxidase inhibitors (MAOI) slow down the progression and improve symptoms of Parkinson's disease Inhibiting MAO-B not only prolongs the half-life of dopamine and extends its neurotransmission effect for relieving motor symptoms, but also prevents the further MAO-B-mediated oxidative damages during dopamine degradation [2] and decrease parkinsonian symptoms [3].

Agents targeting oxidative stress are prime candidates for neuroprotection. Numerous ambitious efforts were made in the search for disease modifying therapies in Parkinson's disease, but clinical trials so far have failed to identify any compound with compelling proof for neuroprotective properties. Despite some advances in symptomatic treatment, the search for neuroprotective agents remains a major challenge for future research

We have delevoped a new class of benzimidazole hydrazones containing hydroxy and methoxy substituents. Their neurotoxicological, neuroprotective and antioxidant properties were studied. The least neurotoxic compounds exhibiting the highest neuroprotective potential were selected to be investigated as potential MAO-B inhibitors. Herein we report their evaluationon on human recombinant MAOB enzyme (hMAOB) (1 μM). These effects were compared with the effect of rasagiline - a potent MAO-B inhibitor used for the treatment of Parkinson's diseases. Administered alone, most of the exam compounds (at concentration 1 μM) didn't revealed statistically significant inhibitory effects on the activity of hMAOB, compared to the control (pure hMAOB). However, some of the compounds revealed statistically significant inhibitory activity on hMAOB that was close to the one of rasagiline.

Acknowledgements: The financial support of The National Scinece Fund of Bulgaria (Contract КП-06-М29/4) is greatly acknowledged.

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RADICAL CYCLIZATIONS OF ALPHA-OXY CARBON CENTERED RADICALS

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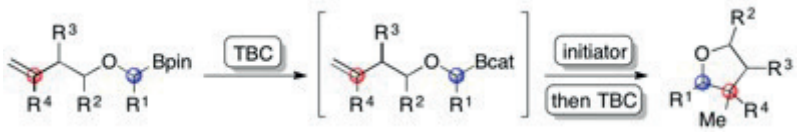
Oxolanes are ubiquitous in natural products and have long been an important class of bioactive heterocycles.[1] These oxacycles are readily accessible via radical cyclization reactions. Despite their importance, only a few papers have reported the cyclization of a-oxy carbon centered radicals, with a majority involving tin reagents.[2,3] Herein, we report a tin-free procedure to generate these radicals that uses air-stable organoboranes as precursors for the rapid construction of decorated oxolane derivatives.



This strategy involves the *in-situ* formation of -oxy catecholboronic ester intermediates to side-step tricky isolations.[4,5] Full details of the method will be disclosed, such as the application to the synthesis of di-, tri- and tetrasubstituted oxolane derivatives, in good to high yields and diastereoselectivities.

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DEVELOPMENT OF NEW BICYCLIC NITROIMIDAZOLES AS ANTITUBERCULAR AND ANTIPARASITIC AGENTS

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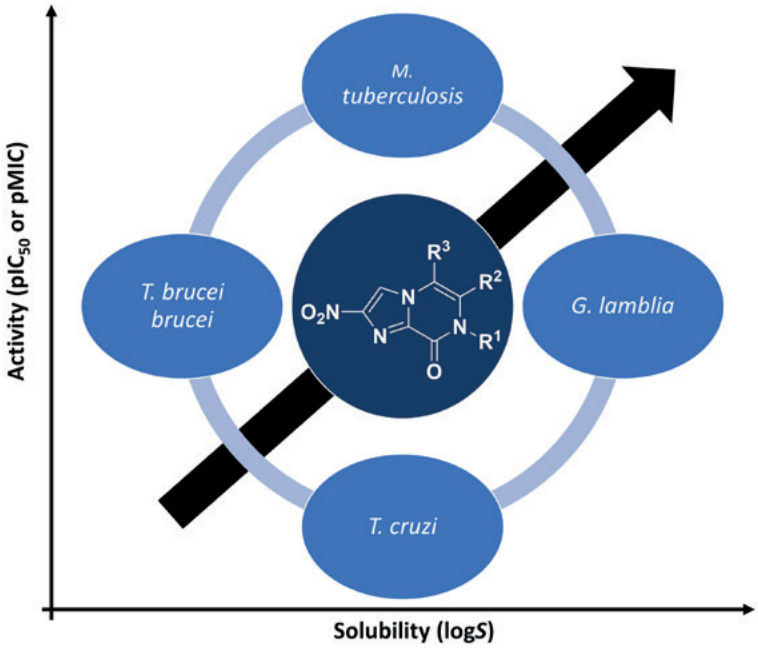
Infectious diseases are a major global health threat, yet the current treatment options are limited and often suboptimal. The nitroimidazoles are an old class of antibiotics that have been widely used to treat infections caused by parasites, mycobacteria, Gram-positive and Gram-negative bacteria.[1] Delamanid and pretomanid, both with bicyclic nitroimidazole core structures, have been developed as new candidates for the treatment of tuberculosis.[2,3] They also have shown repurposing potential against *Leishmania donovani*, the causative agent of visceral leishmaniasis.[4] Inspired by the dual antitubercular and antiparasitic activities of these nitroimidazoles, we have developed a new bicyclic subclass, the 2-nitroimidazopyrazinones[5] with activity against *Mycobacterium tuberculosis*, intestinal parasites (*Giardia lamblia*) and kinetoplastids (*Trypanosoma brucei brucei* and *Trypanosoma cruzi*). Structure-activity relationship (SAR) studies show distinct trends across tested organisms, with tunable selectivity for different pathogens and low cytotoxicity against mammalian cell lines. Selected potent analogues possessed favourable pharmacokinetic profiles with high oral availability. We also describe efforts to improve their solubility without compromising the bioactivity.



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A NEW LIFE FOR DIAZABORINES: THE NEXT GENERATION OF SERINE PROTEASE INHIBITORS

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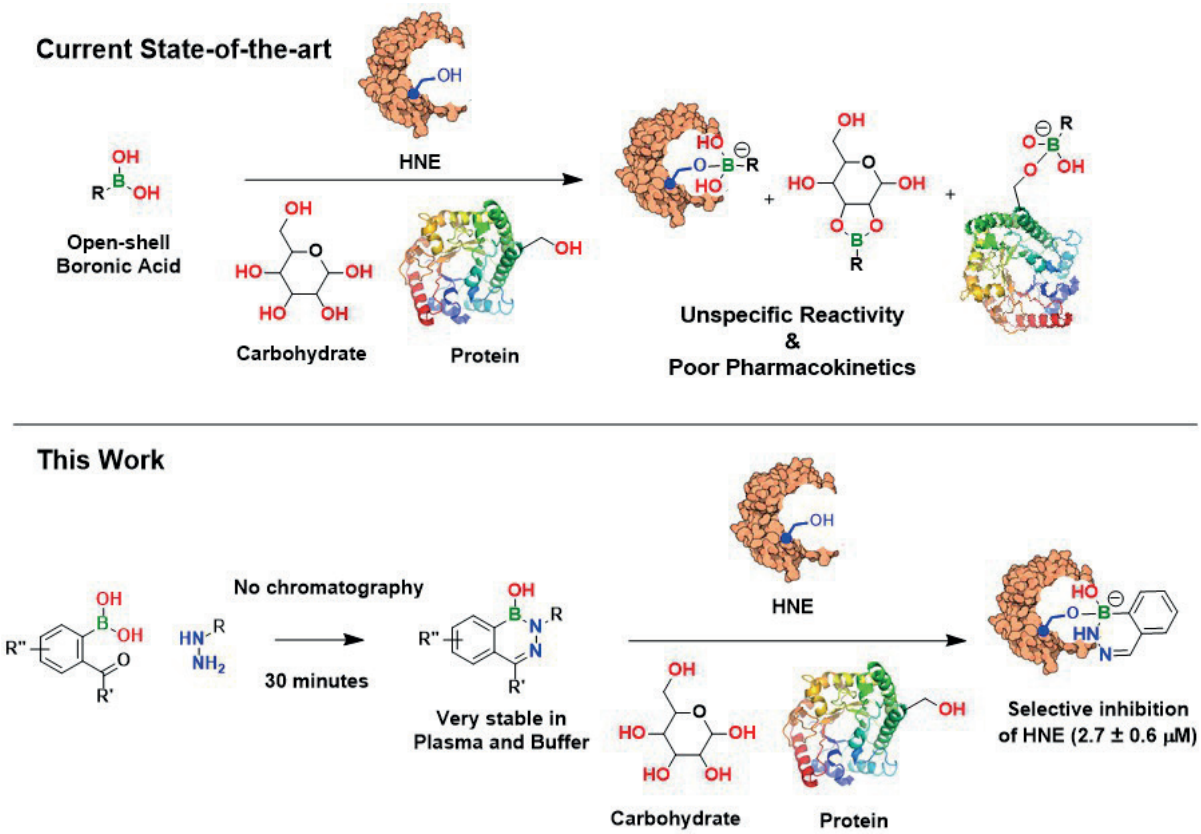
Boronic Acids are a preeminent functionality extensively used to design biologically active compounds such as the FDA-approved Bortezomib and Ixazomib. However, due to boron's open shell, this class of inhibitors also exhibits unspecific reactivity with endogenous nucleophiles that often results in poor pharmacokinetic profiles and off-target toxicity. Here diazaborines are presented as a new class of boron-based warheads for serine proteases inhibition, in which the boron functionality is stabilized in the form of an aromatic BN heterocycle. In this study, diazaborines were readily synthesized in a single step in yields up to 96%, without any chromatographic operation and were shown to selectively inhibit Human Neutrophil Elastase with IC_{50}'s values in the low µM range. Synthetic and theoretical studies performed on this system suggest that, like boronic acids, the reaction mechanism involves the formation of a reversible covalent bond between the diazaborine boron center and the catalytic serine oxygen. Finally and differently from boronic acids who have half-lifes of 2h in buffer, diazaborines were shown very stable in different biocompatible conditions like buffer and human plasma. This work demonstrates that diazaborines are an interesting starting point for the development of the next generation of serine proteases[1].



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IN VITRO EVALUATION OF THE EFFECT OF NEW 1H-BENZIMIDAZOLYL HYDRAZONES DERIVATIVES ON TUBULIN POLYMERIZATION

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The potential of the benzimidazole architecture for the development of novel antineoplastic compounds is well known. Derivatives combining 2-aminobenzimidazole heterocycle and hydrazine fragments have been studied and shown high activity against different cell lines[1-3].Introduction of hydrazone fragments at 1 and 3 position of the 2-imino-benzimidazole heterocycle also lead to promising results[4]. The structural insights gains from these studies provide a good basis for further tuning of the benzimidazole structure and development of new derivatives with improved antineoplastic activity.

Herein we report the synthesis of a series of 1*H*-benzimidazol-2-yl hydrazones, obtained from the coupling of 1 *H*-benzimidazol-2-yl hydrazine with a broad series of hydroxyl and methoxyl-benzaldehydes. The molecular geometry and electronic structure of 1*H*-benzimidazolyl hydrazones were studied based on spectroscopic and computational methods. Using MolInspiration and Toxtree tools, pharmacokinetic characteristics such as lipophilicity, molecular size, flexibility and presence of hydrogen-donor and acceptors, as well as toxicological properties of the newly synthesized compounds were evaluated and provided useful preliminary information.

It is known, that 2-aminobenzimidazole compounds block microtubule function in cells, so that main goal of the investigation was to test the ability of the compounds to inhibit tubulin polymerization. The effect of the 1*H* -benzimidazolyl hydrazones derivatives on tubulin polymerization was evaluated in vitro by using highly purified bovine tubulin with temperature control by spectrophotometric monitoring at 350 nm and compared to nocodazole and paclitaxel as reference.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF BENZAZULENE-BASED COMPOUNDS

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The last report of World Health Organization (February 2018) announced the serious situation in a worldwide anti-microbial resistance (AMR).[1] Drug resistant microbes or 'superbugs' affect not only the human beings but also the animals, food and environment. AMR is major global issue leading to increased health care cost, prolonged hospitality and in many cases to patient morbidity and mortality. The urgent need of discovery and development of a novel antibiotics against resistant pathogens is supported by organizations such as WHO and FDA (U.S. Food and Drug Administration). In this study we are focused on non-heterocyclic fused three-ring azulene system with potential antimicrobial activity on Gram-positive bacteria strains with clinical significance. The interesting chemical properties of benzazulene scaffold as a nucleophile and an electrophile involve the last in numerous chemical reactions.[2-5] Our recent work is focused on oxidation reactions and oxidative amino nucleophilic substitution reactions.[5] We have reported already that benzazulene derivatives exhibit selective inhibitory activity against Pim family members, efficiently impair intracellular anti-apoptotic effect of Pim-1 and Pim-3 and significantly slow down the migration of cancer cells.[4] Therefore, benzazulenes and their derivatives provide a novel group of small molecules with potent anti-bacterial and anti-cancer activity.

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SIMULATIONS OF THE TrkA RECEPTOR TO ELUCIDATE THE MECHANISM OF ACTION OF NEUROTROPHIN MIMETICS

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The tropomyosin receptor kinase A (TrkA) belongs to a superfamily of tyrosine kinase receptors, which when bound to their native ligands, called Neurotrophins, can modulate several signaling pathways that regulate neuronal survival, axonal and dendritic network maintenance, as well as synaptic plasticity.[1,2] Preclinical studies have demonstrated the therapeutic potential of neurotrophins in preventing or slowing down the progression of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and Motor Neuron disease.[3,4] However, the use of neurotrophins as drugs is hindered by their poor pharmacokinetic properties. Therefore, novel, low molecular weight neurotrophin mimetics are promising anti-neurodegeneration drug candidates. Previous studies have identified several steroid compounds with neurotrophin mimetic activity.[5] However, their exact mechanism of action remains unclear. In the present work, molecular simulations of the TrkA receptor have been performed in order to investigate the conformational changes that lead to the activation of the receptor upon Neurotrophin binding. Since the active conformation of the receptor is not known, this study is a crucial step for the examination of the mechanism through which steroidal compounds lead to TrkA activation and the triggering of subsequent signal transduction pathways.

Acknowledgement

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TYROSINASE INHIBITORY EFFECT OF 4H-PYRAN-4-THIONE DERIVATIVES

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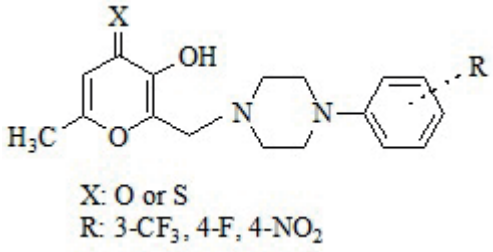
Tyrosinase is a multifunctional copper-containing enzyme, and responsible for melanin production which provides the pigmentation in humans and plants. Although melanin biopolymer is a protective barrier against UV radiation from the sunlight, abnormal accumulation in different specific parts of the skin results in development of freckles, melasma and even skin cancer (1). Therefore, the development of tyrosinase inhibitors has become an issue of great importance and interest in medicinal and cosmetic areas as well as food industry in terms of additives. Kojic acid (5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one, KA) is a well studied fungal agent that exhibits a wide range of pharmacological profile including tyrosinase inhibition. This effect is mainly attributed to copper-chelating property in the active site of the enzyme (2). However, the use of KA is limited due to its cytotoxicity and instability. In order to overcome these problems, many derivatives have been intensively studied. Particularly, KA derivatives containing thioether, sulfoxide, and sulfone groups were shown to demonstrate high antityrosinase activities (3-4). Thus, sulfide linkage found as a critical factor for inhibition activity and without it, it is reported that KA may not bind tightly to the essential parts of tyrosinase. In addition, previously, some Mannich bases of KA derivatives were patented by our research group having potent biological activities including antityrosinase, antioxidant, antiaging and antidermatophytic activities (5).



In this study, we described the synthesis of compounds as allomaltol (5-hydroxy-2-methyl-4*H*-pyran-4-one, ALM) and thio(allomaltol) (5-hydroxy-2-methyl-4*H*-pyran-4-thione) derivatives and evaluated their antityrosinase activity. ALM was synthesized from KA in a two-step reaction–chlorination of KA and subsequently reduction with zinc dust in concentrated hydrochloric acid (6). Mannich bases were prepared from ALM and substituted phenylpiperazine derivatives in the presence of formaline. The chemical conversion of carbonyl to thiocarbonyl compounds was prepared by using Lawesson's reagent (7). Structures of all the targeted compounds were elucidated by IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. The potential mushroom tyrosinase inhibitory activity of the compounds was evaluated by the spectrophotometric method using L-DOPA as a substrate and KA as the control agent. When we evaluated the effect of the replacement of the oxo group with the thioxo function on the antityrosinase activity, we clearly obtained that inhibitory effect significantly increased in 4*H*-pyran-4-thione derivatives.

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OPTIMIZATION OF A NANOMOLAR INHIBITOR FOR THE HEXAMER DNA HELICASE RuvBL1/2 IDENTIFIED IN A DEL SCREEN

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DNA encoded libraries (DEL) have become a valuable platform for hit generation in drug discovery [1]. They provide an efficient and low-cost technology that allow simultaneous screening of large collections of DNA-barcoded small-molecules against a protein of interest using affinity selection protocols. The DNA-tags of the strongest binders are then amplified, and structures are deconvoluted by next generation sequencing. Herein, we report the identification of several structural series of inhibitors targeting the double hexamer complex RuvBL1/2, a DNA helicase that is overexpressed in a variety of human tumor types [2-4] and that had proved to be challenging to target via traditional high-throughput screening methods. We used our YoctoReactor technology to create high fidelity DELs, which were then screened using the Binder Trap Enrichment technology [5], allowing us to identify hits for RuvBL1/2. The most potent hit presented a biochemical IC_{50} of 340 nM and further medicinal chemistry optimization quickly resulted in an improvement of both biochemical and cellular potency. This effort ultimately led to a compound with a cellular IC_{50} of 290 nM. In summary, our unique proprietary technology provided several attractive hits, which proved readily amenable to lead optimization of both physicochemical properties (MW, PSA, logP) and potency.

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GLYCOPEPTIDE ANTIBIOTIC AND SIALIC ACID DERIVATIVES WITH LIPOPHILIC SIDE CHAINS AGAINST INFLUENZA VIRUSES

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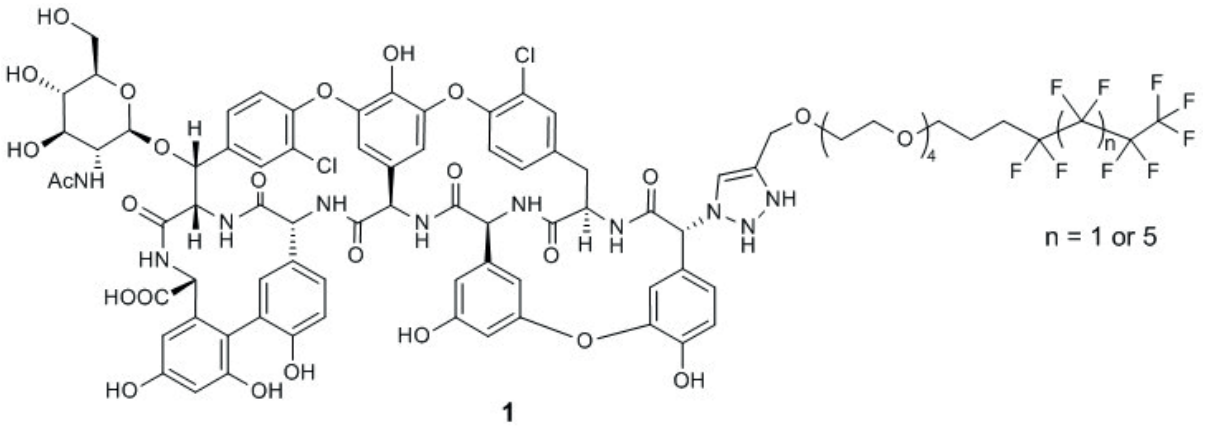
Influenza A viruses cause epidemics annually and serious pandemics occasionally worldwide. Evolution and mutation of the virus result in the loss of the optimal efficacy of vaccines and the development of resistance against antiviral medicines. The generally used neuraminidase inhibitors are not effective enough against influenza viruses, therefore it is essential to find new medications with brand new mode of actions to fight against influenza.

A few years ago we prepared some teicoplanin antibiotic derivatives with lipophilic side chains possessing good activity against influenza strains and a new mode of action [1]. As a continuation of this research we are going to report on the synthesis of new teicoplanin pseudoaglycon derivatives bearing perfluoroalkyl chains as lipophilic substituent (**1**).

Sialic acid glycosides with lipophilic aglycones (**2**) were also prepared and proved to have antiinfluenza virus activity.



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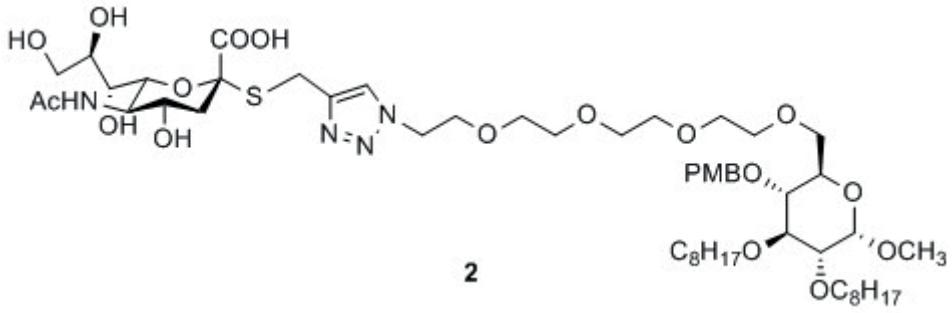

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DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF A RANGE OF NEW BREAST CANCER SELECTIVE AhR LIGANDS

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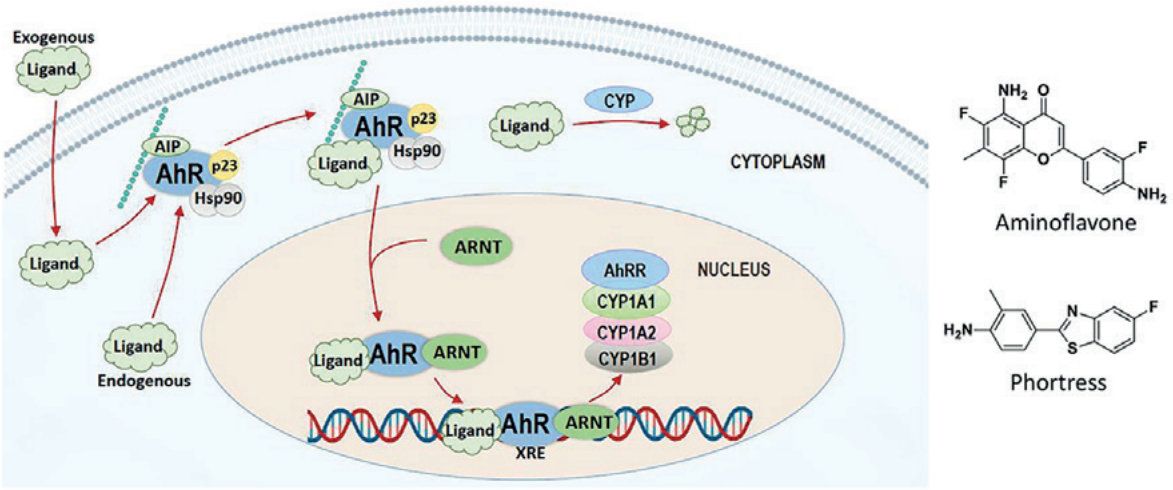
Breast cancer has the second-highest mortality rate among cancers in women; over 2 million women were estimated to be diagnosed worldwide, with over 600,000 deaths anticipated, in 2018 alone.[1] While mortality rates are dropping, incidence rates are rising, with diagnosis rates increasing by 2% per year.[2] In addition, metastatic cancer (Stage IV) remains incurable, with only 25% of patients achieving a 5-year survival rate between 2005 and 2011.[3] Due to increasing rates of resistance to current treatments, as well as the sobering mortality rates for Stage IV sufferers, new treatments and targets are urgently needed. Here we report the targeting of the arylhydrocarbon receptor (AhR) pathway to treat breast cancer. The AhR pathway (Figure below) functions to metabolise toxins via a network of dynamically interacting proteins. Hijacking this pathway results in lethal DNA damage to cells that contain an upregulated AhR pathway; this upregulation is directly related to the sensitivity of the cell lines to these AhR-targeting compounds.[4] A number of breast cancer cell lines have reported upregulation of the AhR pathway up to 10 times higher than related non-cancerous breast cells.[5] Clinical trials have been conducted on previous AhR-targeting drugs, such as Aminoflavone (figure below, top) and Phortress (figure below, bottom).[6] By exploiting this process in breast cancer tissue, a number of sub micro-molar potent cytotoxic agent have been developed that exhibit excellent selectivity to breast cancer cell lines.[7-9] Here we report the molecular-modelling led structure activity relationship development of this range of compounds, which have now produced a number of nano-molar potent inhibitors of breast cancer cell lines, and offer exquisite selectivity over healthy cell lines; this work represents promising future breast cancer treatments.



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SYNTHESIS AND STRUCTURE OF NOVEL 6,7-DIHYDRO-2H-IMIDAZO[2,1-c][1,2,4]TRIAZOL-3(5H)-IMINE DERIVATIVES WITH POTENTIAL ANTICANCER ACTIVITY

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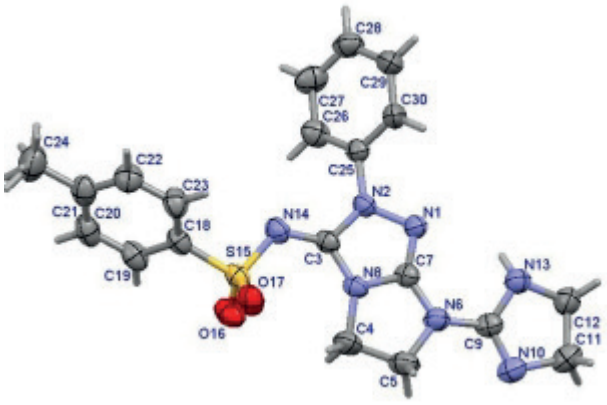
Commonly used antineoplastic drugs represent a group of structurally diverse compounds. Their incomplete efficacy and acquired resistance of tumor cells remain a major challenge in cancer treatment.

The imidazo-triazole scaffold has been found in several promising classes of compounds having an interesting pharmacological profile and broad-ranging applications. They were extensively explored due to their anticancer, antimicrobial, antifungal and antiviral activity [1-4].

As a part of our research aimed at synthesis of novel heterocyclic compounds with anticancer activity [5-8], it has been described a series of 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-imine derivatives.

First, the appropriate *N*-cyano-*N*-arylhydrazines were reacted with 2-chloro-4,5-dihydro-1*H*-imidazole (2-chloroimidazoline) yielding 7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-aryl-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-imines, which subsequently were converted into the corresponding amides and sulfonamides by the treatment with acyl or sulfonyl chlorides. Finally, reactions of 7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-aryl-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-imine derivatives with aryl isocyanates and isothiocyanates gave rise to the formation corresponding ureas or thioureas. Thus obtained novel 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazoles constitute a new chemotype in the anticancer drugs design process.

The structure of the novel 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazolo-3(5*H*)-imine derivatives was confirmed by IR, NMR spectroscopic data. Single crystal X-ray analysis of the newly obtained compounds was performed at the Department of Crystallography, Faculty of Chemistry, A. Mickiewicz University in Poznań. *In vitro* cytostatic activity was investigated at the Department of Medicinal Chemistry, University of Greifswald, Germany and National Cancer Institute, USA.



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SYNTHESIS AND BIOLOGICAL PROPERTIES OF NOVEL 2'-DEOXY-C-NUCLEOSIDES CONTAINING FIVE-MEMBERED HETEROCYCLES

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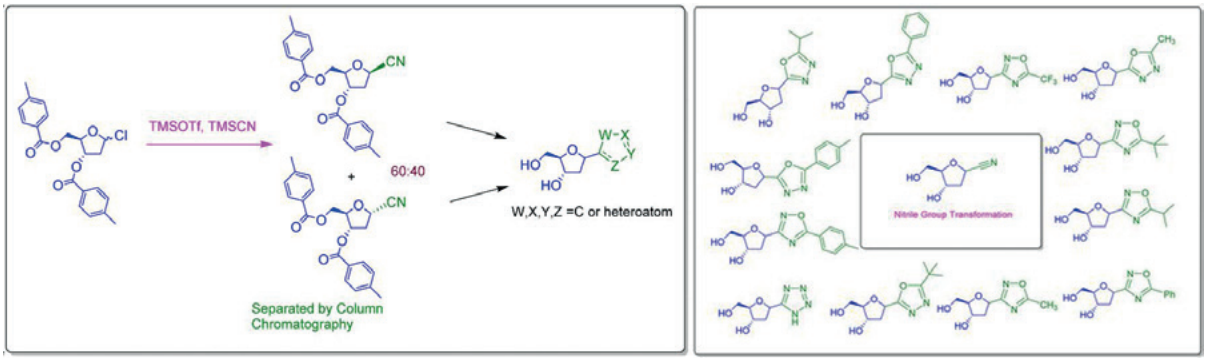
Chemical modification of natural nucleosides has led to the discovery of several commercial drugs as antiviral and anticancer agents. In this vein, C-nucleoside [1,2,3,4] has proven to be valuable molecule due to their natural occurrence, increased stability, altered H-bonding characteristic and unique molecular recognition abilities. Unlike natural and synthetic N-nucleosides, C- nucleosides are stable to enzymatic and acid-catalysed hydrolysis of the glycosidic bond. These properties of C-nucleosides offer a distinct advantage over the N-nucleosides for the design of novel drug like structures.

Herein, we describe a modular synthesis approach allowing rapid assembly of C-nucleoside library in an efficient manner. Synthesis of a common building block by C-C bond formation at C1 and further integration of the heterocycle was key feature of our approach. The glycosyl cyanide is one of the most important type of C-glycosyl intermediate, which is usually obtained as mixture of cyanide anomers from 1-chloro carbohydrates by reaction with trimethyl silyl cyanide in the presence of a Lewis acid as catalyst. These two anomers of glycosyl cyanides were transformed into various C-nucleosides containing five membered heterocycles. The design, synthesis and biological activity [5,6] of these novel C-nucleosides will be presented.



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DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL SMALL MOLECULE INHIBITORS OF CHIKUNGUNYA VIRUS

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The Chikungunya virus (CHIKV) is the causative agent of the Chikungunya fever, an illness characterized not only by a rapid onset of high fever but also by severe myalgia and leads in some cases also to death. Even years after the infection, some patients suffer under recurrent and persistent myalgia, which causes an impaired quality of life. Since its re-emerging in 2005, the disease had massive outbreaks infecting millions of people in more than 40 countries not only in Asia and Africa but also in America and Europe (France and Italy). Currently, there are no specific antiviral drugs or vaccines available to prevent or treat the infection, although the predicted outbreak of a new epidemic in a Mediterranean city like Rome is highly probable. Therefore, the design and development of novel effective antiviral drug compounds are immensely needed. [1, 2, 3, 4]

In 2014, Moesslacher discussed a series of novel small molecules Chikungunya inhibitors. From the starting point CIM016321, a hit discovered by HTS by the Centrum voor Innovatie en Stimulatie van Medicijnonwikkeling (CISTIM) and KU Leuven, she produced a total of 59 analogues in a hit to lead optimization program. [5]

Based on the most effective compounds, a series of new promising molecules was now designed, synthesized and tested against not only the Chikungunya virus but also Enterovirus 71, Zika virus and Norovirus. Hereby, the concept of bioisosterism, the Topliss tree of decision and machine learning program FAME II where used for a systematic variation of substitution pattern. Based on pharmacophore modelling virtual screening is now performed to detect new promising hits for future projects. In addition, the 4-step-synthesis established earlier was optimized, resulting in a higher overall yield.

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DESIGN, SYNTHESIS AND EVALUATION OF 2-BENZYLIDENEBENZOFURAN-3-ONES (AURONES) AS HUMAN PROTEIN KINASE CK2 INHIBITORS

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CK2 is a pleotropic serine/threonine protein kinase. Overexpression and overactivity of CK2 is associating with more than 20 types of cancer. Thus, CK2 is becoming an important target for the treatment of cancer. This has given rise to considerable interest for the design of human protein kinase CK2 inhibitors.

Herein, we report the design, synthesis and SAR studies of 2-benzylidenebenzofuran-3-ones (aurones), a new family of nanomolar ATP-competitive inhibitors of CK2. A series of aurones (51 compounds) were synthesized, structurally related to the synthetic flavones with nanomolar activity which we had developed previously [1, 2]. Further biochemical tests revealed that 20 aurones inhibited CK2 with IC_{50} in nanomolar range of values. Analysis of calculated lipophilic efficiency (CLipE) of identified inhibitors showed that the best CLipE was 4.0 (see CLipE values on Figure 1, red dots). The property-based optimization of aurones was performed, yielding a series of potent CK2 inhibitors with enhanced lipophilic efficiency (see CLipE values on Figure 1, green triangles). The most promising compound **BFO13** had CLipE = 4.94 (CLogP = 3.5; IC_{50}= 3.6 nM).

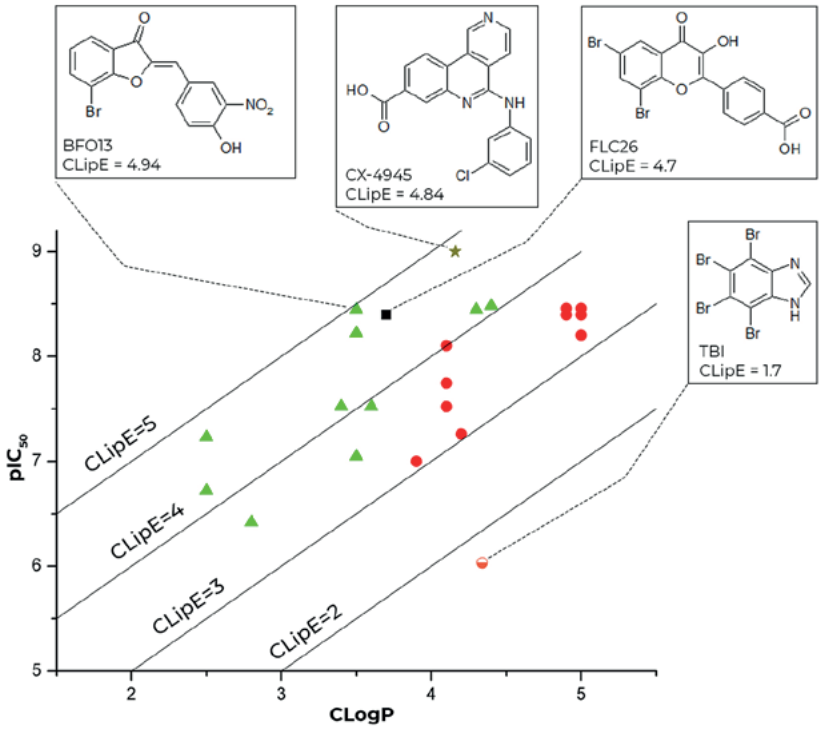

Figure 1. CLipE values and structures of 2-benzylidenebenzofuran-3-ones and well known inhibitors of CK2.

Our research has demonstrated that 2-benzylidenebenzofuran-3-ones have a great potential as CK2 inhibitors. The use of LipE-based optimization with structure based drug design helped to decrease lipophilicity of aurones without a reduction in potency. The obtained inhibitors show low nanomolar affinities for the human protein kinase CK2 and may be of interest for further biological evaluation.

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INSPIRED BY NATURE: STRUCTURE-ACTIVITY RELATIONSHIP OF A FACTOR H-BINDING PEPTIDE TO MODULATE UNDESIRED HOST COMPLEMENT ACTIVITY

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The complement system is a self-amplifying, fast reacting protein network, largely known for its involvement in host defence pathways. However, its importance in pathologies such as transplantation and age-related conditions has been increasingly recognized. Strategies for taming complement attack of host and biomedical surfaces are therefore actively pursued. The strategy we are pursuing drew inspiration from nature: some pathogens are exploiting complement regulators, such as the abundant plasma protein Factor H (FH), by recruiting them to their surface and consequently protecting themselves from complement attack. Our group mimics this strategy by using synthetic entities to tether FH to cellular or artificial surfaces for therapeutic purposes.

Pursuing this idea, a 14 amino acid-long disulphide-bridged cyclic peptide (5C6) was previously discovered by our group through phage display screening. 5C6 showed nanomolar binding affinity to FH and was able to act as a molecular bridge between FH and implant or transplant surfaces when combined with appropriate tethering motifs. For improving affinity and stability of 5C6, we targeted three key aspects: first, we replaced the disulphide with other functional groups such as alkenes, lactams, thioacetals or triazoles, affecting activity to different degrees. Second, we varied the size of the macrocycle, which had a profound impact on activity, enabling us to define the maximally tolerated ring size. Third, we replaced individual amino acids with natural and unnatural amino acids to successfully improve affinity of 5C6. The compounds were prepared by solid-phase peptide synthesis and further modified using solution-phase reactions. Binding affinities were determined by direct surface plasmon resonance binding and competitive microscale thermophoresis assays.

The current study expanded our knowledge about the structure-activity relationship of the FH-binding peptide 5C6, which will facilitate the rational development of protective coating to protect cells and materials from erroneous complement attack.

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OPEN SOURCE MALARIA SERIES 3: A PROMISING AMINOTHIENOPYRIMIDINE LEAD

Mathamsanqa Bhebhe (1), James Cronshaw (1), Alice Williamson (1), Murray Robertson (1), Althea Tsang (1), Angela Butera (1), Matthew Tarnowski (1), Carmen Tran (1), Patrick Thomson (2), Tom Foley (2), Peter Rutledge (1), Matthew Todd (3)

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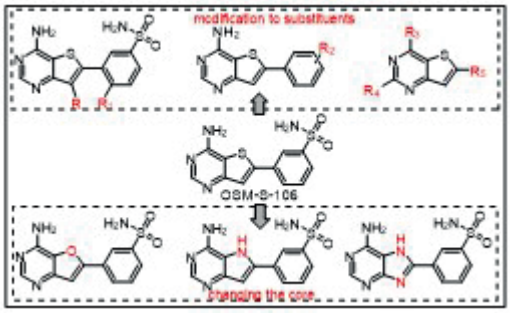
In 2010 GSK released data on 13,500 antimalarial hits. One of these was potent and was used to start Series 3 of the Open Source Malaria Consortium, where the activity was confirmed (OSM-S-106). We will present all the research carried out to date on this aminothienopyrimidine core. All modifications to the substituents have decreased the potency of the drug. We are now conducting SAR studies by changing the core of the original hit compound and seeking the mechanism of action of the series through computational, biochemical and genetic approaches.



NOVEL ARGINASE INHIBITOR OATD-02 ENHANCES ANTI-TUMOR EFFICACY OF CHECK POINT INHIBITORS

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New approaches for cancer treatment using checkpoint inhibitors confirmed that stimulation of antitumor immunity can lead to strong clinical benefits including full regression. Evidence from preclinical and clinical studies demonstrated that interference with multiple immune checkpoints provides a superior efficacy. The role of myeloid derived suppressor cells (MDSCs) are increasingly recognized as an important mediator of tumor immune evasion. MDSCs secrete the enzyme arginase which depletes local arginine concentration. Depletion of arginine represents an important mechanism of immunosuppression, and high arginase (ARG) activity in plasma and tumor demonstrated in patients with a wide spectrum of cancers correlates with a poor prognosis. Arginase promotes the immune escape of cancer cells by decreasing L-arginine concentration which is required for proliferation and activation of cytotoxic T and NK cells. Moreover, some cancer cells release ARG-1-containing exosomes further suppressing antitumor immunity. Restoration of arginine levels in the tumor microenvironment by ARG inhibitors induces T-cell activation and proliferation leading to the T-cell-mediated anti-tumor responses.

We have developed **OATD-02**, a potent small-molecule inhibitor of ARG1 and ARG2 that is now in the IND-enabling GLP studies. Herein, we present a full pharmacological and biological characterization of PK/PD of **OATD-02** and demonstrate its significant antitumor efficacy as a monotherapy and in combinations with checkpoint inhibitors.

OATD-02 is a low nanomolar ARG1/2 inhibitor with good intracellular activity. **OATD-02** restores the proliferative capacity of ARG-1- suppressed human T cells and increased CD3ε and CD3ζ expression. Oral bioavailability of **OATD-02** varies between species (mice, rats and dogs) but in all it exhibits low clearance with long $T_{1/2}$ assuring high compound concentrations exceeding IC_{50} (mouse) and IC_{90} (rats) for 12 and 24 h, respectively after oral administration at a dose of 10 mg/kg. **OATD-02** has a high volume of distribution and reaches high exposure levels in tumors.

OATD-02 shows a sustained, dose-dependent pharmacodynamic response in rats and mice (3 fold increase in the plasma arginine concentrations after a single oral dose of 10 mg/kg) with high arginine level maintained for 24 h indicating a potential for a once a day dosing. The comparison of in vitro and in vivo efficacy of **OATD-02** with the reference compound reveals the superior advantage of **OATD-02** especially at pharmacodynamic effects. Clearly, these two ARG inhibitors have a completely different pharmacological profile. IND submission for **OATD-02** is planned on 2019/2020.

Funding: The research was supported by the National Science and Research Development (NCBIR) STRATEGMED program 2/265503/3/NCBIR/15

3D-FUSED HETEROCYCLES: WHEN FLATLAND MEETS 3D-LAND

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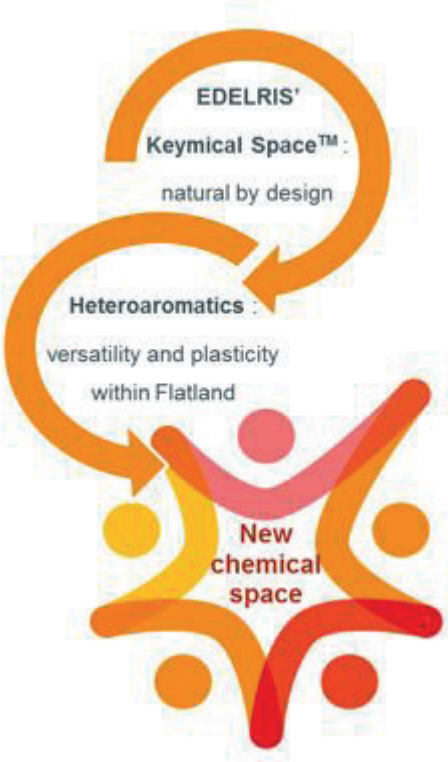
Heterocyclic structures are highly represented in marketed drugs. There are indeed considered as privileged structures [1] in medicinal chemistry in particular for their good metabolic stability and strong capacity to interact with proteins through hydrophobic and/or hydrophilic interactions [2]. However, purely heterocyclic structures have also been associated to a "flatland" that could lead to poor druglike properties and compromise their chance of success in clinical development [3].
Based on its know-how, EDELRIS has recently developed innovative chemistry to bring heteroaromatic moieties into scaffolds with natural product topologies. In contrast to previously reported collections of aromatic and heteroaromatic compounds [4], the flexibility associated with the combination of heterocyclic and stereochemically rich ring systems allows a fine calibration of compound properties and enhance considerably the pharmacophoric diversity achievable to address protein interaction. Our contribution to explore unknown ring systems [5] as well as the tool-box to achieve their efficient synthesis will be presented.



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LIGAND-BASED DISCOVERY OF NOVEL AND SELECTIVE NKCC1 INHIBITORS FOR THE TREATMENT OF CORE SYMPTOMS OF DOWN SYNDROME AND AUTISM SPECTRUM DISORDERS

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Proper GABAergic transmission through Cl-permeable $GABA_A$ receptors is fundamental for physiological brain development and function. Indeed, defective GABAergic signalling, due to a high ratio of the expression of the Cl^- importer NKCC1 and Cl^- exporter KCC2, has been implicated in several neurodevelopmental disorders including Down Syndrome (DS)[1] and Autism Spectrum Disorders (ASD)[2]. Here, we show a ligand-based computational strategy to identify new molecular entities that we tested *in vitro* for their capacity to selectively block NKCC1. We present our extensive synthetic efforts and structure-activity analyses that allowed improving *in vitro* potency, efficacy, and drug-like properties of the initial chemical scaffold. In particular, we generated one lead compound that has excellent solubility and metabolic stability *in vitro*. This lead compound is effective when administered *in vivo*, being able to recover the cognitive deficits in a DS mouse model (Ts65Dn mouse) and social and repetitive behaviours related to autism core symptoms in the valproic-acid (VPA) mouse model of ASD. Importantly, chronic treatment with this compound had no significant diuretic effect and toxicity in adult animals. Our novel, potent and selective NKCC1 inhibitor devoid of diuretic effects may thus lead to a sustainable therapeutic option for the treatment of DS, ASD and possibly many other neuro-pathologies characterized by NKCC1/KCC2 defective ratio.

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SYNTHESIS AND EVALUATION OF 3'-DEOXY-3'-FLUORO-7-DEAZAPURINE NUCLEOSIDES AS ANTIKINETOPLASTID AGENTS

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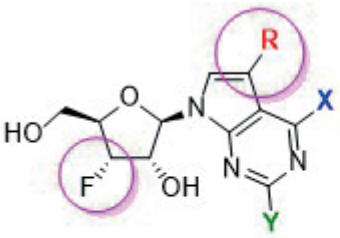

X = NH_2, OMe, OH
Y = NH_2, Me

- 30 compounds
- various C7 substituents
- nM-µM IC_{50} ***T. cruzi, T. brucei, L. inf***

Sleeping sickness, Chagas disease and Leishmaniasis are classified by the WHO as "neglected tropical diseases". They are vector-borne diseases that affect millions of people in the poorer parts of the world and are often fatal if left untreated. Their causative agents are the kinetoplastid parasites *Trypanosoma brucei*, *Trypanosoma cruzi* and

Leishmania spp. respectively. Current therapies suffer from severe drawbacks, incl. toxicity, administration difficulties and low efficacy, highlighting the need for better therapeutics. Like most protozoan parasites, the kinetoplastids are purine auxotrophs and thus rely on the purine salvage pathway as their sole purine source. Interfering with purine salvage is therefore an attractive strategy for the development of new chemotherapeutic agents.

Previously, our group discovered several new nucleoside analogues, derived from the natural product tubercidin (7-deazadenosine) with promising activity against these parasites. Modifications of the sugar (3'-deoxygenation) and C7-substitutions of the nucleobase led to highly potent analogues with reduced toxicity.[1,2] In this work we further investigated modifications of the ribose part. 3'-Deoxy-3'-fluoroadenosine and 3'-deoxy-3'-fluoroinosine have previously been described as antiprotozoal agents.[3] Therefore, we combined the 3'-deoxy-3'-fluororibose modification with a 7-deazapurine nucleobase surrogate. Several substituents were introduced on the C7-position and the C2- and C6-position were derivatized to furnish a collection of adenosine, inosine and guanosine mimicking nucleoside analogues.

The synthesized nucleosides were assayed *in vitro* against *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania infantum.* Several compounds displayed interesting activity, warranting further evaluation *in vivo*.

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TRIAZENE-BASED PRODRUGS FOR SELECTIVE TARGETING OF HYPOXIC SOLID TUMORS

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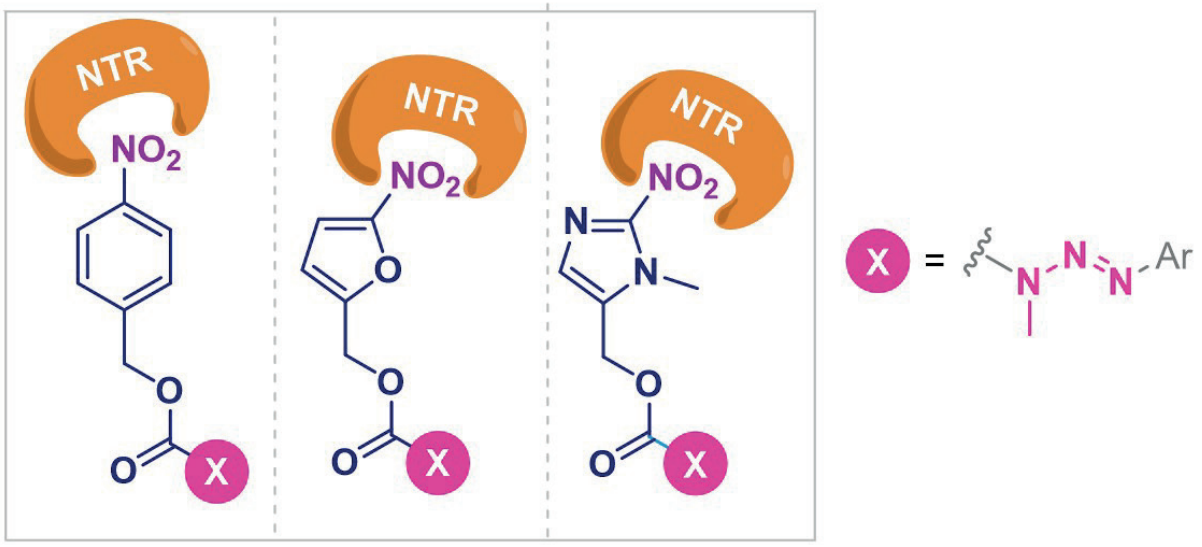
Displaying a broad-spectrum chemistry, triazenes are best known for their cytotoxic properties, as exemplified by dacarbazine and temozolomide, well-known anticancer agents. Triazenes exert their chemotherapeutic activity through a unique mechanism of action that involves formation of a reactive alkyl diazonium intermediate capable of alkylating DNA and promoting cell death.[1] Herein we report a triazene-based platform, **1**, that can be activated by nitroreductases[2] (NTRs) to undergo a self-immolative process that culminates with the release of the cytotoxic triazene. A series of nitro(hetero)aromatic prodrugs **1** (**figure 1**) of cytotoxic triazenes was synthesized and NTR-mediated hydrolytic activation was investigated by HPLC and LC-MS. Corroboration of the reduction reaction was attained through chemical reduction and by means of the synthetic des-nitro analogue. A549 cells (human epithelial lung carcinoma cells) were selected as representative cell lines for bioreductive experiments under normoxic and hypoxic conditions. In addition, a NTR-activated off-on probe for cell imaging was also prepared. These combination of attributes makes bio-triggered triazenes particularly attractive as a novel targeted theranostic approach.



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CHAMPIONING THE UTILISATION OF STATE-OF-THE-ART PHOTOCHEMISTRY AND ELECTROCHEMISTRY METHODS

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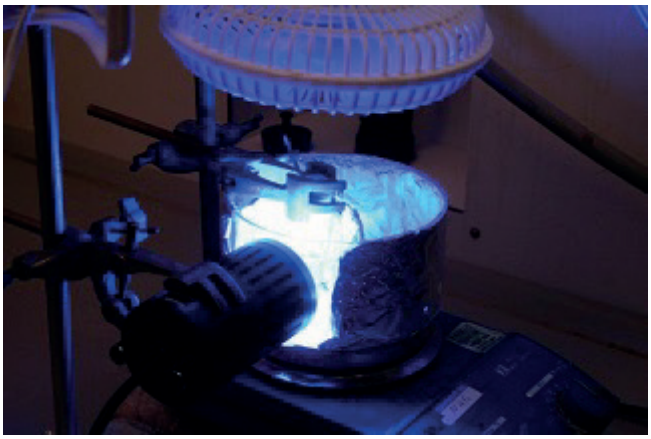
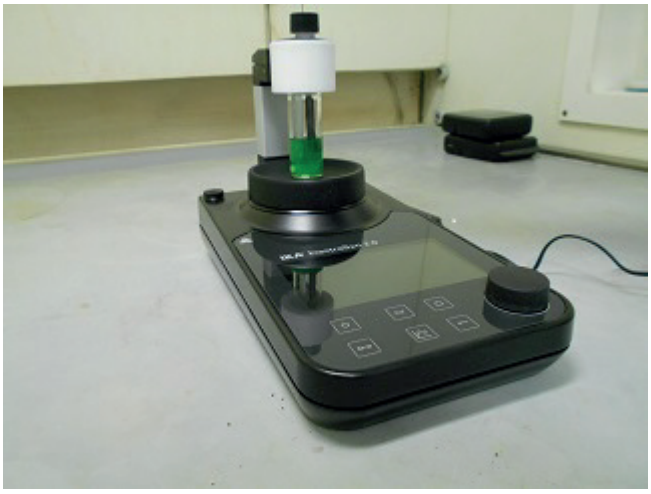
Photochemistry and electrochemistry can facilitate new synthetic transformations that are not currently possible using standard solution-phase organic chemistry. We have sought to increase adoption of new technologies in our chemistry department by repeating literature examples in house and sharing experimental and mechanistic understanding with our colleagues.

Examples will be shown for electrochemistry using the ElectraSyn 2.0 and for photochemistry using equipment developed in-house.





PROTEIN KINASE B (PKB/AKT) TARGETED SMALL MOLECULE COMPOUNDS TO PROMOTE CARDIAC REGENERATION

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Ischemic heart diseases are the leading cause of death worldwide. In an acute myocardial infarction, up to 25% of heart muscle cells i.e. cardiomyocytes (CM) die. Due to the limited renewal capacity of CMs, the infarction often leads to fibrosis and heart failure (1). However, some lower vertebrates and neonatal rodents have an intrinsic regenerative capacity to fully repair the injured heart muscle, which in rodents quickly declines after birth due to irreversible cell cycle arrest of CMs (2). It also seems that humans possess this ability at the time of birth (3). By reactivating the CM cell cycle the damaged area could potentially be regenerated and fatal heart failure prevented. Current treatments for heart failure are mainly palliative with limited effect on prognosis, so there is a pressing need for more effective therapies.

Signaling pathways mediated by protein kinase B (PKB/AKT) are known for antiapoptotic and cell proliferation-promoting activities in various cell types, including CMs (4). AKT activators could thereby potentially enhance the proliferation of CMs after myocardial infarction. SC79 (Figure 1) is a known small molecule PKB/AKT activator, which however is chemically and metabolically labile for degradation (5). Moreover, SC79 has tautomeric forms, which further complicate the identification of binding interactions with its target PKB/AKT. In this study, we design and synthesize SC79 derivatives by altering its substituent pattern and core structure. The aim of the study is to find more stable SC79 derivatives, which activate PKB/AKT, and to investigate their effects on CM viability and cell cycle.

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SYNTHESIS AND BIOLOGICAL PROPERTIES OF NOVEL ARGINASE INHIBITORS

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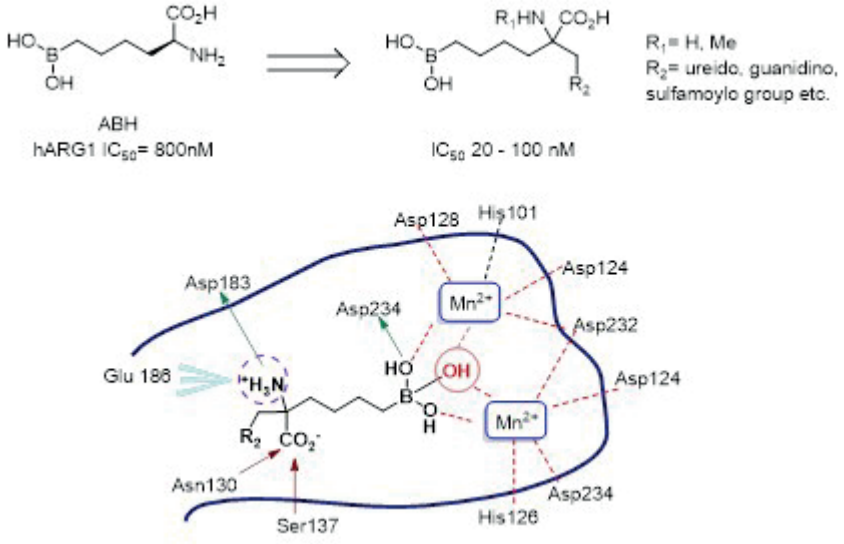
Arginase is a manganese-dependent enzyme that hydrolyzes arginine to ornithine and urea. Two isoforms of this protein are known (ARG-1 and ARG-2) and both catalyze the same reaction, but the localization of the enzyme isoforms in cellular environment is different: ARG-1 is a cytosolic protein and ARG-2 is localized in mitochondrial matrix [1]. Elevated arginase activity has been implicated in pathology of multiple disorders like asthma, pulmonary hypertension, hypertension, T-cell dysfunction, erectile dysfunction, atherosclerosis, renal disease, ischemia reperfusion injury, neurodegenerative disease, wound healing, inflammatory disease and fibrotic disease [2]. Arginase also promotes the immune escape of cancers by decreasing level of arginine that is required for proliferation and activation of cytotoxic T and NK cells. High plasma and tumor arginase (ARG) activity have been demonstrated in patients with a wide spectrum of cancers and correlated with a poor clinical prognosis and a refractory disease.[3]

Working on the new anti-cancer immunotherapies, we discovered a novel class of small-molecule inhibitors of arginase [4]. Herein we present, results of our early studies. Based on the well-known 2-(*S*)-amino-6-boronohexanoic acid (ABH) arginase inhibitor [5] we designed and synthesized a series of compounds with basic and neutral side chains in the α-position related to amino acid functional group. *In vitro* structure-activity relationship (SAR) data, general synthetic pathway, asymmetric synthesis as well as PK/PD profile of selected compounds will be presented.



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TARGETING HIF-1α SIGNALING IN BREAST CANCER BY 6-AMINODERIVATIVES OF QUINOXALINE-2-CARBONITRILE 1,4-DIOXIDE

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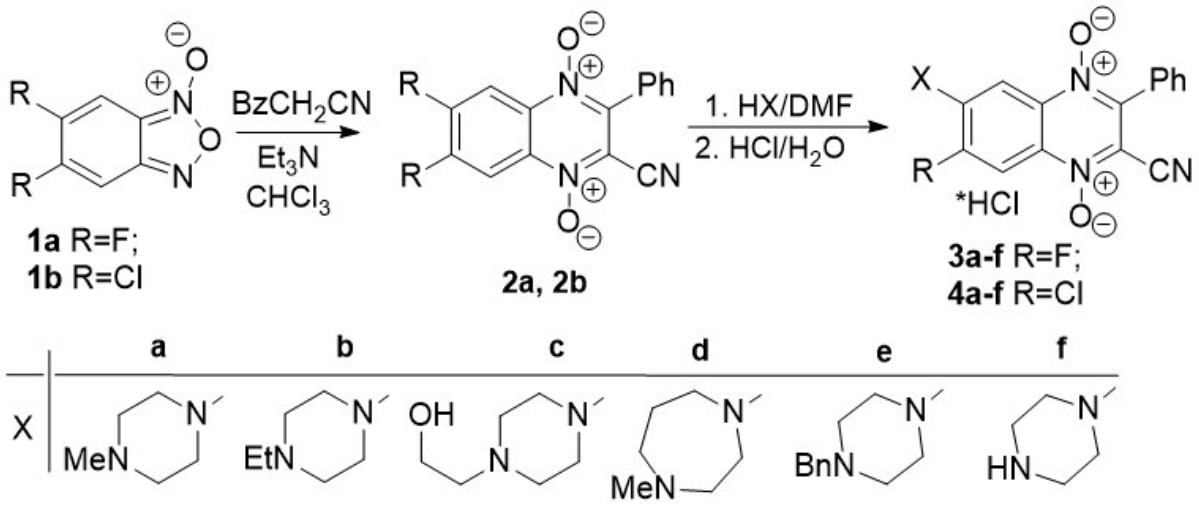
Quinoxaline 1,4-dioxides are the promising class for targeting hypoxia pathways in tumor cells [1]. So, we aimed to obtain new water-soluble derivatives of 6-amino-7-halogenoquinoxaline 1,4-dioxides for the inhibition HIF-1α signaling, a key path of hypoxic metabolism, in breast cancer cells.

The starting 6,7-dihalogeno-3-phenylquinoxaline-2-carbonitrile 1,4-dioxide (**2a, 2b**) was obtained by the condensation of appropriate benzofuroxanes **1a-b** and benzoylacetonitrile in chloroform in the presence of triethylamine [2]. The selective substitution of 6-halogen atom by cyclic diamines afforded the derivatives **3a-f**, **4a-f**. All synthesized compounds were characterized by NMR-spectra and UV spectroscopy, HRMS. The purity of the compounds was >95% as determined by HPLC analysis. The antiproliferative activity of novel quinoxaline-2-carbonitrile 1,4-dioxides was evaluated in normoxia (N, 21%O_2) and hypoxia (H, 1%O_2) by MTT test after 72 h cell growth. HIF-1α and AP1 activity was assessed by reporter analysis.



Series of 6-amino-7-halogenoquinoxaline 1,4-dioxides demonstrated high antiproliferative potency and hypoxia-selectivity towards hormone-dependent and triple negative breast cancer cell lines (MCF-7, MDA-MB-231). MCF-7 cells were more susceptible to these agents both under hypoxia (IC_{50} = 0.2-2.3 μM) and normoxia conditions (IC_{50} = 0.6-7.9 μM). Antiproliferative activity of the most potent compound **3f** for MCF-7 cell line (IC_{50} = 1.9/0.2 (N/H) μM) was in 10-25 times higher than for the reference drug tirapazamine (IC_{50} = 24.2/4.5 μM). Selected lead-compounds **3f** and **4f** showed inhibitory effects on HIF-1α and AP1-dependent luciferase activity, while tirapazamine revealed no potency to block these factors in MCF-7 breast cancer cells.

Novel 6-amino-7-halogenoquinoxaline-2-carbonitrile 1,4-dioxides showed potent antiproliferative activity, hypoxia-selectivity and promising HIF-1α inhibitory effects in breast cancer cells. The experiments were supported by RFBR grants 18-53-34005 (chemistry), 18-015-00422 (biology).

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THE DEVELOPMENT OF SUBTYPE-SELECTIVE NMDA RECEPTOR COMPETITIVE ANTAGONISTS TO STUDY THE MECHANISMS OF LEARNING AND MEMORY

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We have developed a series of *N*-Methyl-D-aspartate receptor (NMDAR) competitive antagonists with high subtype-selectivity 1) to be used as pharmacological tools to study the different NMDAR subtypes and their involvement in mechanisms of learning and memory, and 2) as lead candidates in the development of therapeutic agents to treat diseases associated with these brain functions.

NMDARs are a family of ionotropic glutamate receptor expressed in the central nervous system (CNS). They are typically comprised of tetrameric combinations of two subunits, GluN1 and GluN2. These receptors have important roles in memory and learning[1], and are implicated in several neurological disorders. They are therefore a desirable pharmacological target, however few NMDAR drugs, and no competitive antagonists, have passed the clinical trial process. This is thought to be due to a lack of selectivity; NMDAR subtypes involved in vital brain function are inhibited as well as those involved in neurological disorders, leading to adverse side effects.

The neurotransmitter (*S*)-glutamate binds to the GluN2 subunit, of which there are four subtypes: GluN2A, GluN2B, GluN2C and GluN2D. These subtypes are differentially distributed within the CNS and endow NMDARs with different physiological properties. To date, the design of GluN2 subtype-selective competitive antagonists has been largely unsuccessful, due to high GluN2 subunit sequence homology and a lack of structural information. Even so, compounds with modest selectivity are widely used as tool compounds, highlighting the demand for such agents.

We have previously developed competitive antagonists which show moderate selectivity for GluN2C/D subtypes (e.g. PPDA[2,3], UBP141[4] and UBP145[5]). Using molecular modelling and structure-activity relationship studies, we have now developed a series of novel competitive antagonists based on these compounds, a number of which show significantly improved selectivity for GluN2C/D, and the first in this series to exhibit GluN2A selectivity.

These new compounds will be valuable tools for studies of NMDAR function. Given the improved selectivity, which would likely be associated with an improved adverse effect profile, they may also be important leads for the development of drugs to treat disorders in which NMDARs are implicated, such as dementia and neuropathic pain.

This work was funded by the BBSRC grant number BB/L001977/1 and the National Institute of Mental Health of the National Institutes of Health under Award Number R01MH060252.

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ANTIMYCOBACTERIAL ACTIVITY AND METABOLISM OF (PHOTO)SWITCHABLE N-SUBSTITUTED AZAAURONE E- AND Z-ISOMERIC FORMS

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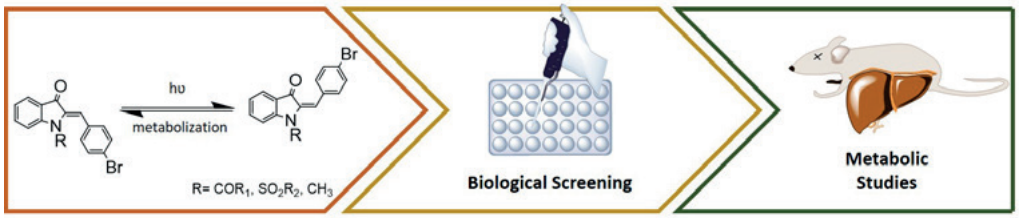
Tuberculosis stands as one of the most lethal diseases worldwide, with 1.6 million deaths reported in 2017. [1] Regarding current therapies, the emerging resistance alongside low therapy compliance are key factors in increasing disease burden and mycobacteria proliferation. [2] It is urgent to find new potent drugs against *Mycobacterium tuberculosi*s, that may overcome the resistance problem and simplify the treatment.

Azaaurones are potent antimycobacterial agents, with MIC_{99} values as low as 0.37 μM against *M. tuberculosis H37rv* strain [3]. SAR analysis revealed that *N*-acetyl azaaurones display improved activity when compared to their NH counterparts, while being rapidly metabolized. *N*-Acetyl azaaurones are typically synthesized as inseparable mixtures of the *E* and *Z* isomers. We now report, for the first time, the synthesis, photoisomerization, biological evaluation, and metabolism study of the *E* and *Z* isomers of diversely *N* -substituted azaaurones. Metabolic- and photoisomerization studies reveal that the stereoelectronic properties of *N*-substituent play a determinant role in the isomerization rates. Here, we also disclose the structure-activity and structure-metabolism relationships for these novel antimycobaterial agents.



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STEROIDAL AROMATASE INHIBITORS: C-6ALFA OR C-7ALFA SUBSTITUTION?

Carla Varela (1,2), Fernanda Roleira (1,2), Cristina Amaral (3), Saul Costa (2), Georgina Correia-da-Silva (3), Natércia Teixeira (3), Elisiário Tavares da Silva (1,2)

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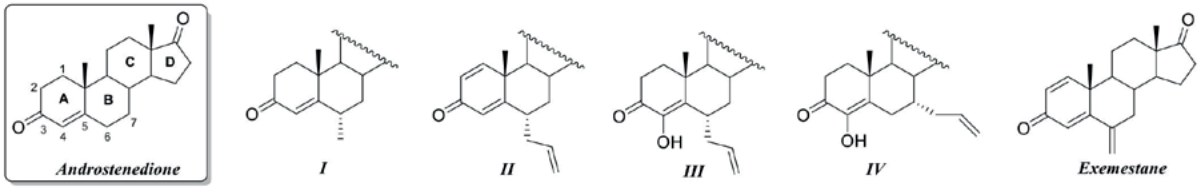
Breast cancer has been identified as the 2ndmost frequently diagnosed cancer among women[1]. In the majority of cases, it depends essentiality on estrogens for its development. Suppressing estrogen in circulation will prevent new cases and also allow regression of established ones. This is better achieved inhibiting estrogen biosynthesis through aromatase. Therefore, aromatase inhibitors (AIs) play a very important role in the treatment of ER+ breast cancer. Some of our former work[2]has given new insights about the importance of functionalizing the C-6 and C-7 positions of androstenedione, the natural substrate. In this work, two series (methyl and allyl) of C-6alfa and C-7alfa derivatives were synthesized based on the most potent hits we have previously prepared[3], especially with C-3 or C-4 or C-1 and C-4 double bonds or epoxide functions. The inhibitory activity then was evaluated in human placental microsomes as well as in MCF-7aro breast cancer cells and results have recently been published [4]. Among the methyl series, C-6alfa derivatives revealed to be better AIs with ***I*** as the most potent. In the allyl series, C-6alfa substitution was also better than C-7aalfa leading to the best AI found, compound ***II***. This compound combines structural features known to afford significant inhibitory activity, namely the carbonyl group at C-17 and the double bond at C-4[3]. Besides, it also has an additional carbonyl group at C-3 and a conjugated double bond at C-1 which makes derivative ***II*** very similar to exemestane, the steroidal AI in clinical use. In our work, we found an unusual behaviour when comparing the pair ***III/IV*** in which the C-7alfa derivative is the strongest. Contributing to this effect, the C-4 substituent appears to interfere with the interaction of C-6 substituent with the access channel of the active site of aromatase. This makes the C-7 substituent more suitable for the referred interaction, increasing the activity of ***IV*** comparatively with ***III***. Despite this exception, results allowed concluding that it is better to functionalize position C-6 than C-7, and that the methyl group seems to be the best substituent to achieve powerful aromatase inhibition.



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NEW AMINO SUGAR-BASED NAPHTHOQUINONES AND ISOQUINOLINE-5,8-DIONES AND THEIR HALOGENATED COMPOUNDS: SYNTHESIS, ANTIBACTERIAL EVALUATION AND IN SILICO ADMET STUDIES

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Antibiotic resistance has emerged as a serious global public health problem and lately very few antibiotics have been discovered and introduced into clinical practice.[1] Therefore, there is an urgent need for the development of antibacterial compounds with new mechanism of action, especially those capable of evading known resistance mechanisms. In this work two series of glycoconjugate and non-glycoconjugate amino compounds derived from of isoquinoline-5,8-dione **1a-d** and 1,4-naphthoquinone **4a-d** and their halogenated derivatives **2a-d**, **3a-d**, **5a-d** and **6a-d**, respectively (**Figure 1**) were synthesized and evaluated for antimicrobial activity against Gram-positive (*Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *S. simulans* ATCC 27851) and Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Proteus mirabilis* ATCC 15290, *Klebsiella pneumoniae* ATCC 4352 and *Pseudomonas aeruginosa* ATCC 27853) strains of clinical importance. This study revealed that glycoconjugate compounds derived from halogeno-substituted naphthoquinones **5a-c** and **6a-c** were more active against Gram-negative strains, which cause infections whose treatment is even more difficult, according to the literature.[2] These molecules were also more active than isoquinoline-5,8-dione analogs **1-3** with minimum inhibitory concentration (MIC = 4-32 µg/mL) within Clinical and Laboratory Standard Institute[3] MIC values (CLSI 0.08-256 µg/mL). Interestingly the minimal bactericidal concentration (MBC) values of the most active compounds were equal to MIC classifying them as bactericidal agents against Gram-negative bacteria. Sixteen compounds among eighteen carbohydrate-based naphthoquinones tested showed no hemolytic effects on health human erythrocytes whereas more susceptibility to hemolytic cleavage was observed when using non-glycoconjugate amino compounds. *In silico* Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) evaluation also pointed out that these compounds **1-6** are potential for oral administration with low side effects.[4] In general, this study indicated that these compounds should be exploited in the search for a leading substance in a project aimed at obtaining new antimicrobials more effective against Gram-negative bacteria

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HETERO-DIELS-ALDER REACTIONS OF NOVEL 3-TRIAZOLYL-NITROSOALKENES AS AN APPROACH TO FUNCTIONALIZED 1,2,3-TRIAZOLES WITH ANTIBACTERIAL PROFILE

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The 1,2,3-triazoles are not natural products but have been investigated against several therapeutic targets related with important disease, including antibacterial.[1-3] On the other hand, the hetero-Diels-Alder reaction of conjugated nitrosoalkenes, is an interesting synthetic strategy to functionalized 1,2,3-triazoles.[4] In this context, we decided to focus on the generation and reactivity of 3-triazolyl-nitrosoalkenes towards heterocycles as an approach to new functionalized 1,2,3-triazoles and evaluate their antibacterial profile in Gram-positive (*Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *S. simulans* ATCC 27851 and Methicillin-resistant *Staphylococcus aureus*) and Gram-negative (*Enterobacter cloaceae* ATCC 23355, *Serratia marcencens* ATCC 14756*, Escherichia coli* ATCC 25922, *Proteus mirabilis* ATCC 15290, *Klebsiella pneumoniae* ATCC 4352 and *Pseudomonas aeruginosa*ATCC 27853) strains. Among the eleven derivatives tested, **13** showed selective activity against three reference *Staphylococcus* species. Interestingly, **13** also showed antibacterial activity (8-12 mm) against MRSA (BMB9393) strain collected from hospital patients. The results showed MIC of 32-256 μg/mL against all four bacterial strains, which is within the CLSI range of the antibiotics current on the market (0.08-256 μg/mL). The effects of **13** on *in vitro* biofilm formation showed that 1/4 and 1/2MIC concentrations reduced biofilm formation in a range of 73-76% (p13, showed a percentage of lysis less 10% in all concentrations tested (10-200 μg/mL). In order to theoretically evaluate the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) parameters, **13** was submitted to an *in silico* evaluation in comparison with antimicrobials of clinical use. The analysis revealed that **13** was similar to most of commercial antibacterial with no risk detected for the parameters analyzed. In view of the observed results it can be concluded that **13** presented an antibacterial profile against *Staphylococcus* strains of clinical importance that should be further explored on designing new prototypes.

Keywords: 1,2,3-Triazoles; pyrrole; Diels-Alder reaction; α-bromooximes; antibacterial.

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ANTIPARASITIC HYBRIDS DERIVED FROM QUINOLINE AND TERPENYLNAPHTHOHYDROQUINONES

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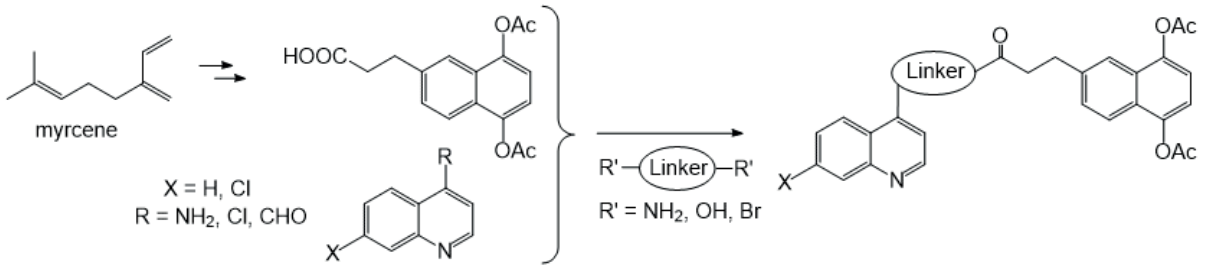
Molecular hybridization is a classical strategy in Medicinal Chemistry that combines the structural characteristics of two or more molecules of natural or synthetic origin to obtain what is called hybrids or conjugates. The conjugates usually improve the bioactive properties of their components separately.[1] In this sense, our research group has been involved for years in the design, synthesis and biological evaluation of new terpenylquinones/hydroquinones, which can be considered hybrids of natural terpenoids and quinones. We have obtained many derivatives that showed very interesting properties as cytotoxics, antifungals and antivirals.[2]

Other bioactivities found in the literature for quinones[3] are antiplasmodial or antimalarial, bioactivities that are also common in quinoline-based drugs. Quinoline is a heterocyclic ring present in many natural and synthetic compounds displaying a wide range of biological activities such as antimalarial, antibiotic, antifungal, anthelmintic, anti-inflammatory or antitumor, among others.[4] Many hybrids of quinoline with other biologically active derivatives have been described, but not with a naphthoquinone moiety. This fact prompted us to design and prepare a new family of hybrids between our terpenylnaphthohydroquinones and quinolines and to explore its potential as antiparasitic. We are interested in the strongyloidiasis, a neglected tropical disease caused by nematodes of the Genus *Strongyloides*. The drug of choice for the treatment is ivermectin, however ivermectin ineffectiveness and drug resistance have been reported and this make necessary to look for new effective drugs.[5] The general structure of the new hybrids is shown in the following figure.



The conjugates between quinolines and terpenylnaphthoquinones were prepared starting from different substituted quinolines and the natural monoterpene myrcene. Both fragments were joined by aliphatic linkers through amine, amide or ester bonds. The cytotoxic and nematocidal results obtained are presented and discussed in this communication.

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TOWARDS THE SYNTHESIS OF NOVEL PROTEASE INHIBITORS: LATE-STAGE MODIFICATIONS ALLOWING DIVERGENT SYNTHESIS FROM PEPTIDE-CARBOXYLIC ACIDS

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Protease inhibition is an emerging and promising tool in the development of novel antivirals. Orthosteric protease inhibitors are often peptide-like molecules mimicking fragments of the protease natural substrate. Inhibition is generally attained introducing on the carboxylic acid terminus of the peptido-mimetic backbone reactive moieties towards the active site of the protease (covalent inhibitors) or unreactive amide bioisosters (non-covalent inhibitors). Library generation of such inhibitors is often hampered by the need of centering the synthesis on the first amino-acid derivative, forcing the chemist to tailor-make each compound since the very beginning. Herein we present the successful development of a library of viral protease inhibitors stemming from the late stage functionalization of peptide-carboxylic acids, deploying the most recent developments in organic synthesis.

DESIGN AND SYNTHESIS OF 4-THIATOCOPHEROL/HYDROXYTYROSOL HYBRIDS AS PROTEASOME ACTIVATORS

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Aging is a natural, inevitable progressive deterioration of physiological function with increasing age for any organism. Aging and longevity are controlled by a multitude of molecular mechanisms and signaling pathways combined with endogenous and exogenous factors in order to maintain cellular homeostasis. Protein homeostasis (proteostasis), is the cellular process that controls the accumulation of damaged or misfolded proteins that contributes to aging and age-related diseases such as Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis.[1,2]

The identification, labeling and degradation of non-functional proteins or normal proteins that have completed their mission is achieved through specific degradation mechanisms such as the **U**biquitin **P**roteasome **S**ystem (UPS) or the lysosomal system. The UPS is the primary pathway for the degradation of normal, damaged or non-functional structures in eukaryotic cells. Regulation of proteasome function may prolong life expectancy by delaying the onset of symptoms associated with proteasome disorders[3]. Thus, the development of new compounds that can activate the main proteasome core, namely, 20S complex may result in beneficial and/or therapeutic effect against human aging and/or in age-related diseases and pathologies.

The present work involves the design and synthesis of new bio-inspired 4-thiatocopherol/ hydroxytyrosol hybrids. Hydroxytyrosol, is the main antioxidant phenolic constituent of olive oil and structural component of oleuropein and 4-thiatocopherol is a bioisostere of the chroman ring of Vitamin E. The two pharmacophores were connected through five-membered heterocyclic rings which are bioisosteres of the amide or ester bonds or possess biological activity. The new compounds were examined for their proteasome activating properties (a) *in cellulo* in human primary HFL-1 fibroblasts and (b) *in vitro* through direct activation of highly purified 20S proteasome and initial results are promising.[4]

Acknowledgement

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IN SITU SYNTHESIS OF METAL-ORGANIC FRAMEWORK AND COVALENT ORGANIC FRAMEWORKS MATERIALS ON THE INNER WALL OF CAPILLARIES AS NOVEL STATIONARY PHASES OF CAPILLARY ELECTROCHROMATOGRAPHY FOR PHARMACEUTICAL ANALYSIS

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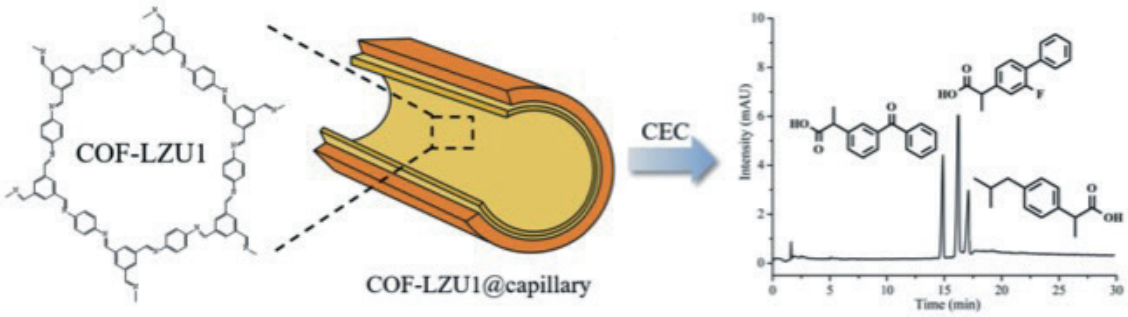
This work will present in situ synthesis of metal-organic framework (MOFs) and covalent organic frameworks (COFs) materials on the inner wall of capillaries as novel stationary phases of capillary electrochromatography for pharmaceutical analysis in our group. We have sucessfully developed a serious of novel stationary phases for capillary electrochromatography, including Zr-based metal-organic framework of UiO-66-NH2, imine-based covalent organic framework LZU1 and TpPa-1 as stationary phases. It has been demostrated that these COFs and MOFs-based stataionary phases show exceptional separation selectivity toward different category of drugs and food additives. High separation efficiency have been achieved as well. Figure 1 shows the covalent organic framework (COF-LZU1) was in situ synthesized on the inner wall of capillary column for electrochromatographic separation of nonsteroidal drugs and amino acids. In this talk new approaches in my research group will be presented.



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SYNTHESIS AND BIOLOGICAL EVALUATION OF DEPUDECIN ANALOGUES

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(-)-Depudecin (**1**) (**Figure 1**), isolated from the culture broths of the fungus *Alternaria brassicicola,*[1] and later, from the weed pathogen *Nimbya scirpicola,*[2] has been identified as a selective inhibitor of histone deacetylases (HDAC) with an IC_{50} in the low μM range.[3] In contrast to representative HDAC inhibitors, depudecin represents a unique inhibitor of these enzymes by virtue of its molecular structure, featuring the presence of two oxirane rings separated by a *trans* double bond. Originally discovered as part of a biological screening directed towards the identification of antitumour agents with detransforming activity,[4] depudecin was identified as a bioactive metabolite capable of reverting the transformed morphology of tumor cells. This biological activity elicited a great biomedical and biological interest by virtue of its potential as an antitumor agent as well as for further understanding the biological roles of HDACs. Depudecin induced not only morphological changes but also cell cycle arrest and cellular differentiation,[5] and also exhibited remarkable anti-angiogenesis activity.[6] Prompted by its striking biological properties and enticing structure, we decided to initiate a research program directed towards the synthesis of natural depudecin. Our synthetic plan has recently culminated with linear and convergent total syntheses.[7]

Now, we have synthesized an array of depudecin analogues, including truncated and stereoisomeric analogues. With the aim to explore their biological activity, we have performed preliminary biological evaluations, which consisted of the measurement of the antitumor properties of the generated analogues against a panel of various tumor cell lines, including the human promyelocytic leukemia (HL60), human breast adenocarcinoma (MDA-MB-231), human fibrosarcoma (HT1080) and gioblastoma (U87MG), as well as a primary culture of nontransformed bovine aorta endothelial (BAEC) cells, which may indicate a putative antiangiogenic effect.[8] In this communication we report the synthesis and biological activity of an array of depudecin analogues which led us to a structure-activity relationship (SAR) study of this intriguing natural product.

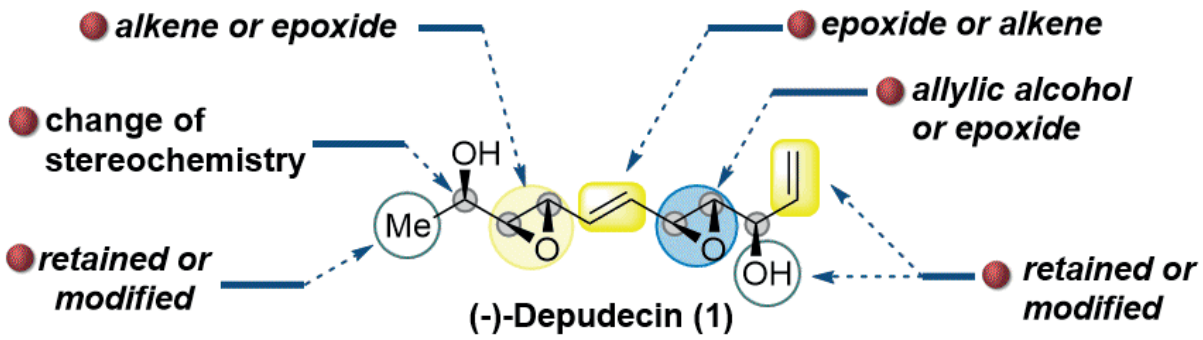

Figure 1. Structure of (-)-Depudecin and Proposed Analogues for SAR study.

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NEW ENANTIOPURE HYDROXYETHYL-PIPERAZINES AS CARBONIC ANHYDRASE INHIBITORS

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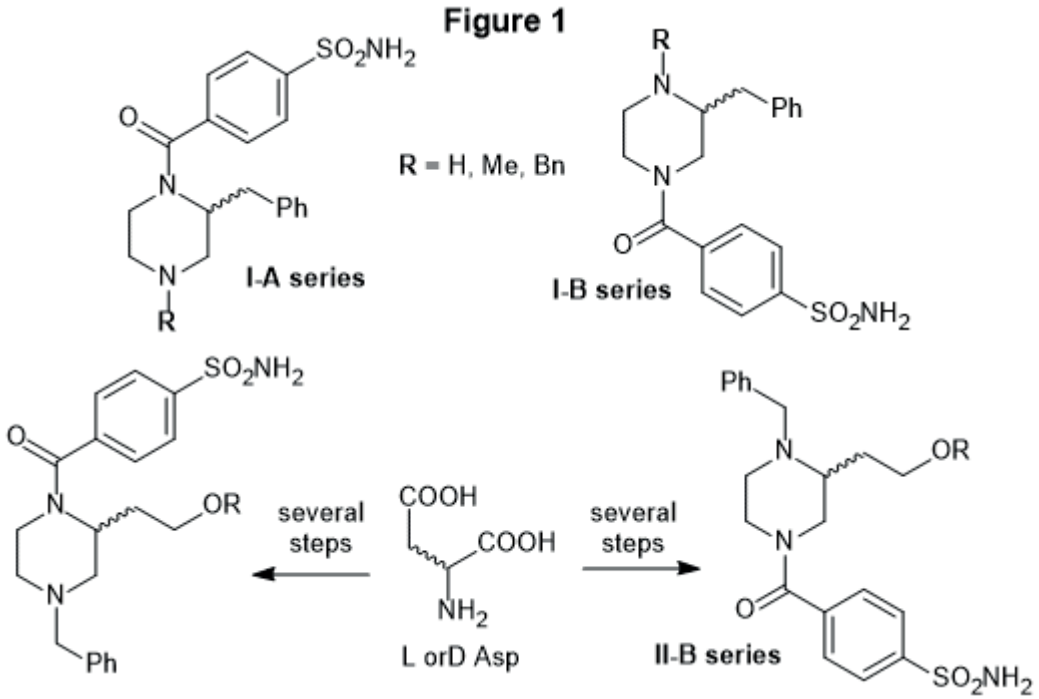
The hydration of CO_2 into bicarbonate and protons and the optimal equilibrium between these chemical species is essential for the vitality of organisms in all life kingdoms [1]. This reaction is catalyzed by the metalloenzyme Carbonic Anhydrase (CA), one of the most efficient enzyme known in nature, evolved in seven genetically different families (α-θ). A large number of isoforms are described among the different organisms, their presence being crucial for pH regulation, secretion of electrolytes and for other essential physiological or pathological processes [2]. For these reasons, CAs are important targets for drugs that can be used for different pathologies, providing that it could be possible to exploit the existent differences between families or isoforms to achieve a selective activity. This may not be an easy task, since the catalytic sites are well conserved, at least among the sixteen human α isoforms (I-XVI); however, variability can be found in hydrophilic and lipophilic accessory sites close to the Zn-binding domain.

Aiming to further investigate the structure activity relationships (SAR) of a previously synthesized series of CA inhibitors **I-A** and **I-B**, bearing an enantiopure benzyl-piperazine scaffold [3], two series of new chiral hydroxyethyl-piperazine **II-A** and **II-B**, carrying a 4-sulfamoylbenzoyl moiety on one nitrogen (**Figure 1**) have been designed and prepared from L or D Aspartic Acid [4]. In this communication the synthesis and inhibitory activity of the new compounds, assessed against four physiological relevant human CA isoforms (I, II, IV, IX), will be reported and compared to the already characterized benzyl-piperazine analogues **I-A** and **I-B**.

Figure 1



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NEW SMALL-MOLECULE DUAL INHIBITORS OF THE p53–MDM2/X INTERACTIONS TO REACTIVATE THE p53 PATHWAY

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Cancer is still the major global health problem with high mortality rate. The search for more effective therapeutic approaches featuring alternative or synergistic anticancer agents with minimal side-effects continues.

The p53 protein has an important role in the tumor suppression and regulation of cell processes and, nowadays, it is well established that the p53 signaling pathway is activated under cellular stress.Although, the p53 inactivation due to negative regulation by the proteins MDM2 and MDMX is a common event in 50% of human cancers.[1] In the last years, medicinal chemistry approaches to regulate the p53 pathway have been mainly focused on inhibiting the p53-MDM2 interaction, however, it is now clear that for targeting effectively the p53 pathway it is required the dual inhibition of p53-MDM2/X interactions.[2]

To address this challenge, in the last years our group has been working on the development of MDM2/X dual inhibitors. A preliminary screening of enantiopure tryptophanol derivatives in yeast cell models led to the identification of a hit tryptophanol-derived oxazoloisoindolinone.[3] In search of more potent p53 activators, an optimization process was carried out in order to improve the anticancer activities of the hit compound. In this communication, we will present our most recent results related with the lead generation. The chemical libraries of enantiopure tryptophanol derivatives were easily obtained through a chiral-pool cyclocondensation strategy, in good to excellent yields. This synthetic approach is highly efficient and an economic way to obtain enantiopure compounds.

The anticancer activity of the new compounds was studied in HCT116 cells with wild-type p53 and respective p53-null isogenic derivative cells. Two compounds were identified as selective p53-activators. Both compounds were able to cause growth inhibition, mediated by p53 stabilization and upregulation of p53 transcriptional targets involved in cell cycle arrest and apoptosis, in wt p53-expressing tumor cells (including MDM2- or MDMX-overexpressing cells). The results also indicated that the tryptophanol-derived small molecules potentially activated p53 by disruption of the p53-MDM2/MDMX interactions.[4-5] *In vivo* studies using human tumor xenograft mice models confirmed a p53-dependent antitumor activity of tryptophanol derivatives through induction of apoptosis and inhibition of proliferation and angiogenesis.[4]

Therefore, tryptophanol-derived compounds can be considered promising drug candidates for the treatment of cancer and a good starting point to develop more potent anticancer agents based on the p53 activation.

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NEW STRATEGIES TO CONTROL TRANSLATION EFFICIENCY BY OLIGONUCLEOTIDES AGENTS

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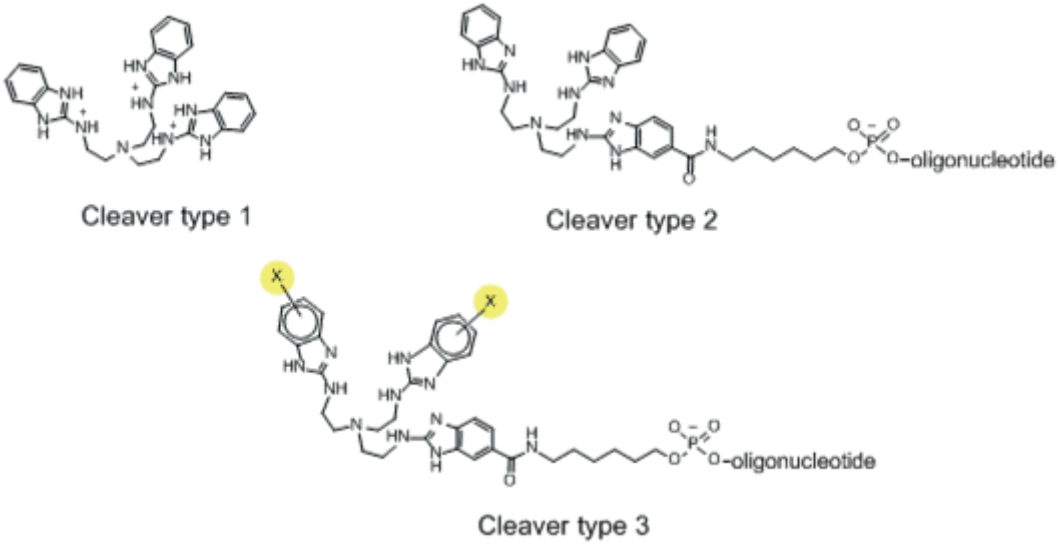
Tris(2-aminobenzimidazoles) **1** have been recently identified as powerful cleavers of ribonucleic acids. [1] The reaction involves nucleophilic attack by the 2'-hydroxy groups at phosphorus and the formation of 2',3'-cyclic phosphates.[2] Thus, this catalyst is completely specific for RNA and does not hydrolyze DNA. [1] Unfortunately, tris(2-aminobenzimidazoles) tend to aggregate in a pH-dependent way, thereby preventing deeper mechanistic insight from pH-rate correlations and similar experiments.[3,4,5]

In this project, we describe the conjugation of this catalyst with a series of DNA oligonucleotides. The resulting conjugates **2** efficiently cleave complementary RNA strands at submicromolar concentrations in the expected positions. They do not aggregate and allow to complete the characterization of benzimidazole derived RNA cleavers.

However, the major aim of this project is rate optimization of the catalyst. This has been done by:

1. Adding electron donors and acceptors in order to modulate the pKa of the catalysts **3**.[3]
2. Synthesizing PNA conjugates. These molecules consist of RNA cleavers conjugated to oligonucleotide analogues such as peptide nucleic acids (PNAs). The benefits of this category is improved resistance against biodegradation and the higher affinity to RNA. Moreover, the addition of two or even more Lys residues in the peptide sequence increase the positive charge of the molecule then due to electrostatic interactions with the membrane of the cell we expect an improving entrance of the catalyst molecule to the cell.[6]



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SYNTHESIS AND BIOLOGICAL EVALUATION OF CHROMANE DERIVATIVES AS S1P1/5 RECEPTOR AGONISTS FOR TREATMENT OF MULTIPLE SCLEROSIS

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Multiple Sclerosis(MS) is a neurodegenerative autoimmune disorder of the central nervous system. The FDA-approved Fingolimod is the first oral drug for relapsing forms of MS. Following phosphorylation in vivo, an active form of Fingolimod acts as a sphingosine 1 phosphate (S1P) receptor modulator by binding with high affinity to S1P receptors (S1P1,3~5). Although it shows high efficacy for treatment of MS, the non-selective activity of this compound for S1PR3 causes serious side effects such as bradycardia.

Our therapeutic strategy is to lower the circulating lymphocytes more efficiently by internalization of S1P1 on lymphocyte, and to enhance remyelination by modulation of S1P5 on oligodendrocytes.

In this study, we have designed a new series of S1P1 and S1P5 receptor agonists on the basis of the structure of ono-4641 and A-971432. The preliminary in vitro evaluation of the synthesized compounds using calcium mobilization assay showed that their agonistic effects agonist S1P1 and S1P5 are comparable to those of other reported agonist ligands. In addition, we performed β-arrestin internalization and recruitment experiments of hit compounds to verify their β-arrestin dependent signaling pathway. Indeed, KKSM08024 showed 98% and 51% activation values at the concentration of 10μM respectively for S1P1 and S1P5 receptor. EC50 value of KKSM08024 was 0.157±0.016μM, which is comparable to that of BAF312 (0.103±0.009 μM), a second generation MS drug developed by Novartis. Further evaluation and synthesis of these compounds regarding selectivity between S1P1 and S1P5 will also be presented.

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NOVEL MOLECULES POTENTIALLY RELIEVING DISORDERS CAUSED BY NMDA RECEPTOR HYPOFUNCTION. STRUCTURE-ACTIVITY RELATIONSHIP

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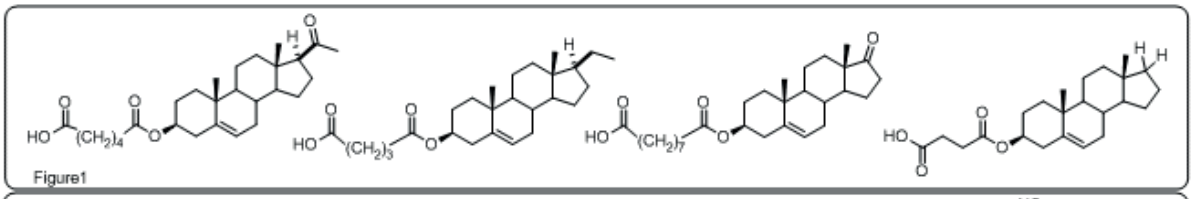
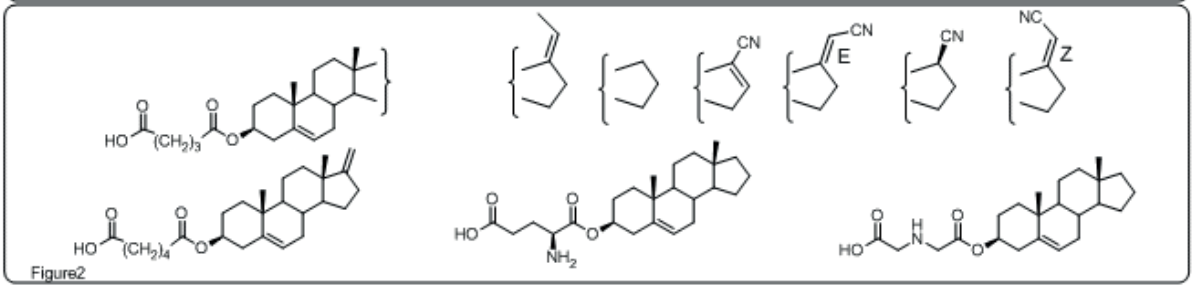
Neurosteroids are endogenous molecules modulating several types of neuronal receptors. For example, 3b-Hydroxy-5-pregnen-20-on sulfate potentiates responses mediated by the NMDA receptor, the most abundant receptor for the excitatory neurotransmitter, glutamic acid. Hypofunction of this receptor is connected with many neurological disorders such as intellectual disability,[1] autism spectrum disorder,[2] or schizophrenia.[3] The finding of small molecule potentiating NMDA receptor function is a challenge for medicinal chemistry.

We have designed, and synthesized series of modified neuroactive steroid analogs with estrane, androstane, and pregnane skeleton, based on our knowledge of structural requirements targeting desired biological activity. An extensive study on the structure-activity relationships of NMDARs steroidal positive modulators has been done and partially published by our group **(Figure 1**).[4] Moreover, we have prepared novel compounds**,** not published yet, **(Figure 2),** which exert interesting positive allosteric NMDA modulating effects.

We will present the results of the SAR study, the synthetic approach and activity assay of the most active NMDA receptor potentiators.





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THALIDOMIDE-RESEMBLING NEW DICARBOXIMIDES SHOW ANTICANCER AND IMMUNOMODULATORY ACTIVITY VIA TARGETING ABCF1 PROTEIN

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Novel derivatives of dicarboximides were found to be selectively toxic towards human chronic myelogenous (K562), acute myelogenous (HL-60) and acute lymphoblastic (MOLT-4) leukemia cells while non-toxic to normal primary human endothelial cells (HUVEC).[1,2] The reported IC_{50} values for dicarboximides in K562 and HL-60 cells were similar or lower to IC_{50} of registered drugs, as cytarabine, sorafenib or irinotecan. Dicarboximides **7, 9** and **10** induced apoptosis in K562 and MOLT-4 cells via receptor and mitochondrial pathways. Specifically, compound **9** induced cleavage of caspase 8 and 9 while compound **7** increased the expression of several proapoptotic genes involved in both, receptor *(*e.g. *TNFRSF 10A, TNFRSF 10B, CASP8)* and mitochondrial (e.g. *BAX, BID, NOXA, APAF1)* pathways of apoptosis. Similarly to thalidomide, dicarboximides **7, 9** and **10** occurred to be immunomodulators and reduced the amount of IKZF1 and IKZF3 transcription factors in K562 and MOLT-4 cells. Using a biotinylated derivative of **10,** ABCF1 protein was identified as a target for dicarboximides. Cancer cells with knocked down ABCF1 showed increased resistance to dicarboximides.

New, lead dicarboximides with potent anticancer activity were identified. They showed significant cytotoxicity against cancer cells, especially leukemias and induced apoptosis via receptor and mitochondrial pathways. Tested dicarboximides exhibited immunomodulatory activity in leukemia cells. ABCF1 protein was identified as a target for dicarboximides.

This research was supported by the Polish National Science Centre grant OPUS 2014/15/B/NZ7/00966.

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THE CONCISE, CONVERGENT SYNTHESIS OF SIMPLIFIED TACCALONOLIDES: MICROTUBULE STABILIZERS WITH POTENT ACTIVITY AGAINST TRIPLE NEGATIVE BREAST CANCER

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For decades, natural products have severed as a source for many of the most important drugs on the market. One particular class of natural products that has been of great importance in the field of cancer therapy is microtubule stabilizing agents (MSA). In particular, the taxane class of MSAs are some of the most successful treatments for solid tumors; however, their use is limited by the development of resistance in tumor tissue. The taccalonolide (tacca) class of natural products from the *Tacca* species of plants have nanomolar potency and efficacy against clinically relevant models of taxane-resistance *in vitro* and *in vivo*. Like the taxanes, the taccas have microtubule-stabilizing activity but act by a distinct mechanism involving a covalent interaction with β-tubulin. While highly potent, particularly *in vivo*, the clinical development of the taccas has been hampered by the fact that their chemical structure is too complex for an economically viable synthesis. Herein, we present the development of a synthetic route to simplified tacca analogs that will enable an investigation into the structural basis for the microtubule stabilizing effects of the taccas in an effort to discover a synthetically viable lead compound for drug development. Furthermore, taking inspiration from the taccas structure, a new class of compounds displaying cytotoxicity against clinically relevant triple negative breast cancer cell lines has also been developed. These compounds act by a different mechanism than microtubule stabilization, thus, represent a new avenue of drug discovery inspired by the chemistry of natural product synthesis.

UNDERSTANDING AND EXPLOITING THE ISOMERISATION OF VINYL TO ALLYL SULFONES

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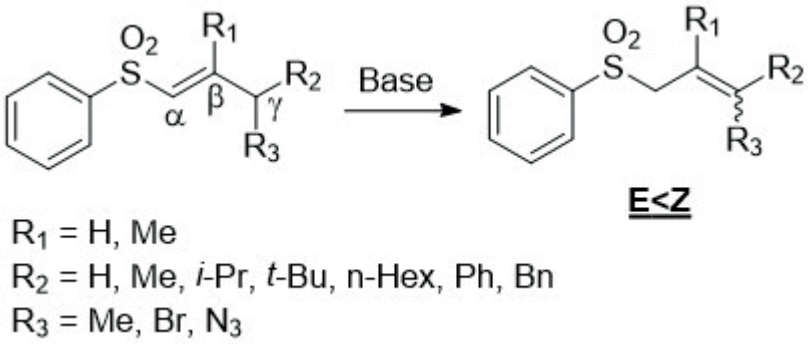
Readily accessible vinyl sulfones can be converted, via a base mediated process, into the corresponding allyl sulfones. In the case of γ-mono substituted vinyl sulfones moderate to excellent selectivity for the *cis*-allyl sulfone can be obtained.[1] This selectivity appears to be highly dependent on the nature of the substituent attached to the γ-carbon atom. Where the substituent is a bromine atom, or methyl group only moderate selectivity is observed. In contrast, when the substituent is an azido group almost exclusive formation of the *cis* -isomer is observed. The origin of this marked selectivity is of interest to us both synthetically and theoretically.



Herein, we describe our ongoing work in this area. Included are the synthesis of a series of γ-mono, γ-di and β,γ-substituted vinyl sulfone precursors which are subsequently isomerised to a series of the corresponding allyl sulfones. These allyl sulfones have been used to synthesise a series of vinyl azides which are currently being applied to the synthesis of enamides, a prevalent motif in the synthesis of natural products.[2] DFT calculations have been used to study the origin of this selectivity and to probe the synthetic space associated with the isomerisation.

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SYNTHESIS OF ANTI-INFLAMMATORY AND PRO-APOPTIC CYCLOPENTENONE PROSTANOID MIMICS

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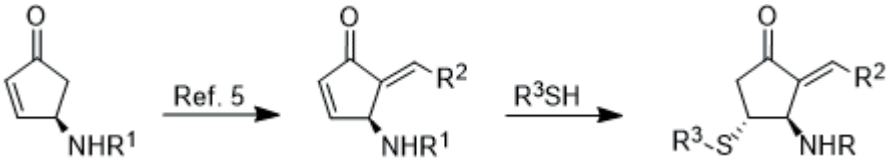
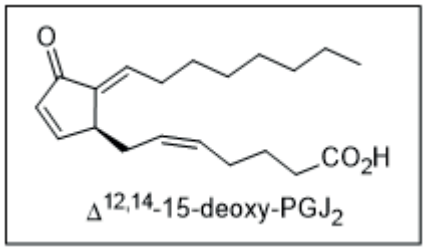
Prostaglandins (PGs) are naturally occurring structures containing 20 carbons, derived from arachidonic acid.[1] They play key roles in the control of inflammation and immune response.[2] It has been indicated that cyclopentenone PGs activate Heat Shock Factors (HSF) and inhibit nuclear factor κ-B-dependent transcription.[3] Upregulation of NF-κB is associated with many tumour types and often leads to poor prognosis for treatment of certain cancers. Unfortunately, many natural PGs are not attractive drug candidates due to poor physiochemical properties. For this reason, the preparation of simpler analogues which are easier to synthesise yet still retain their anti-inflammatory and pro-apoptic properties have been investigated. Previous efforts have focused on the modification of the side chains with an aim of improving the stability and potency of the compound.[4]



The synthesis of 4-aza cross conjugated cyclopentenones, inspired by the PG $\Delta^{12,14}$-15-deoxy-PGJ_2, is described. Current work into the optimisation of a Baylis-Hillman type reaction[5]to install the exocyclic alkene is discussed. Using this technique, a range of aldehydes may be used to mimic the ω-side chain of natural prostanoids. The presence of the 4-amino substituent allowed for derivatisation of the compounds, installing the α-side chain. Research in to masking the electrophilic atom with a sulphur atom will also be discussed.



The library of 4-amino functionalised cyclopentenones along with their cysteine adducts were tested for both inhibition of NF-κB and activation of HSF.

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IDENTIFICATION OF POTENT AND SELECTIVE INHIBITORS OF PHOSPHOINOSITIDE 3-KINASE-BETA (PI3Kb) FOR THE TREATMENT OF PTEN DEFICIENT TUMORS

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The PI3K pathway mediates cell signaling in response to stimulation by growth factors and promotes key cellular functions, such as, survival, proliferation and growth. Dysregulation of the PI3K pathway is one of the most common causes of tumorigenesis and aberrant pathway activation occurs frequently through loss of the tumor suppressor protein, PTEN in several solid tumor types including prostate cancer. In localized prostate cancer an estimated 15% of patients possess a PTEN deficiency while in metastatic castration-resistant prostate cancer, it is estimated that a higher percentage of patients present with PTEN loss.

PI3K lipid kinases comprise isoforms α, β, δ and γ that have distinct roles within PI3K signaling and normal physiology. The PI3Kβ isoform has been implicated as the key PI3K isoform required for driving PTEN deficient cancers.

In a quest to identify potent and selective PI3Kβ inhibitors active in PTEN deficient prostate tumors, we have designed and optimized imidazo[1,2-*b*] pyridazine derivatives into highly potent PI3Kβ isoform inhibitors demonstrating minimal activity against other isoforms and inhibiting cellular p-Akt content in PC-3 cell line, a prostate tumor cell line that is PTEN deficient. Challenges overcome during optimization of Structure Properties Relationships in this series, culminating into the identification of a potential pre-clinical candidate, will be presented.

NOVEL POLYFUNCTIONALIZED INDOLES AGAINST BLOOD STAGE MALARIA PARASITES

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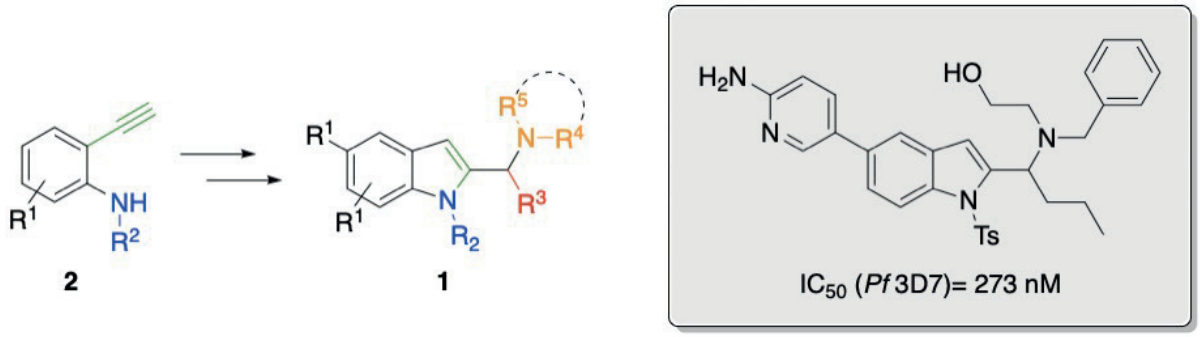
Indoles represent an important structural scaffold for the discovery of new drug candidates, being considered priviledged structures for medicinal chemistry.[1] Several examples of this class have revealed antimalarial activity[2] and some have been included in the pathogen box.[3]
In this communication, we report the results from a structure-activity relationship study, based on the optimization of an early indole hit with promising antimalarial activity against blood stage *Plasmodium falciparum* parasites. The facile access to a small library of polyfunctionalized C2-indoles **1** was explored using a domino multicomponent reaction with the corresponding ethynylaniline **2**, eventual Suzuki coupling and tosyl-deprotection (**Scheme 1**). Our current lead compound revealed to be active against drug-sensitive and drug-resistant malaria parasites at a sub-micromolar range, with IC_{50} values lower than the most active C2-indole included in the Pathogen Box.[3]



Scheme 1 Facile synthesis of polyfunctionalized indoles **1** from the corresponding ethynylaniline **2**

Acknowledgements
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ABSTRACT CANCELLED

THE ADENYLATE-FORMING ENZYME SUPERFAMILY: ACYLATED SULFONAMIDE ADENOSINES AS POTENT INHIBITORS

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The adenylate-forming enzymes catalyze the formation of a highly reactive mixed phosphoanhydride-linked nucleoside intermediate. Numerous members of this structurally diverse family play key roles in a variety of metabolic pathways, making these enzymes excellent drug targets [1,2]. Competitive bioisosteric inhibitors are commonly utilized to inhibit this whole family of enzymes.

High affinity inhibitors of the aminoacyl-tRNA synthetases (aaRSs), important enzymes for protein translation [2], are the aminoacyl-sulfamate nucleosides (aaSAs, Figure 1A). However, they are prone to *N*-cycloadenosine formation and therefore, we generated stable acylated sulfonamide adenosines (aaSoHAs, Figure 1A) using an improved synthetic procedure [3]. The two prepared inhibitors target IleRS and SerRS, which are structurally distinct representatives of Class I and II aaRSs. Key steps in obtaining the SoHA scaffold proved to be a Wittig-Horner reaction and the work-up procedure following an anhydrous, acidic deprotection reaction in order to avoid nucleoside decomposition.

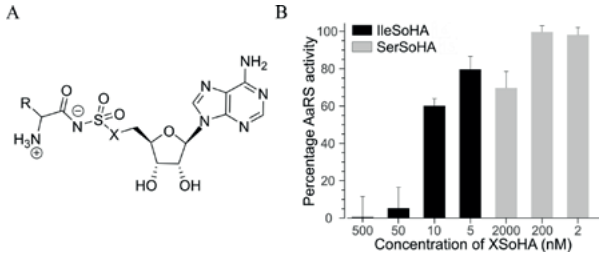

Figure 1: (A) X = O: high affinity competitive sulfamate inhibitors (aaSAs) of aaRSs, X = C: hydrolytically stable sulfonamide inhibitors (aaSoHAs), R = Amino acid side chain; (B) Aminoacylation activity of E. coli IleRS and SerRS in presence of the respective sulfonamide linked intermediate analogue.

The activity of IleSoHA and SerSoHA was compared to their sulfamoyl analogue, exposing an almost complete loss of activity for the latter (Figure 1B). A 2.1 Å crystal structure of SerRS in complex with SerSA was determined and used as a template to model SerSoHA in the active site (Figure 2A). An energetically unfavourable eclipsed conformation was predicted in contrast to Class I aaRS sulfonamide inhibitors, where only staggered interactions were observed (Figure 2B). The same modelling strategy was finally applied to representative members of the whole adenylate-forming enzyme superfamily. The outcomes suggest that, other than for the structural and functional orthologues of the Class II aaRSs, the oxygen to carbon substitution should generally preserve the inhibitory potency.

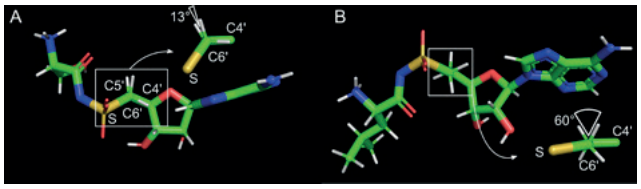

Figure 2: (A) Model of SerSoHA based on the pose of SerSA, bound to K. pneumoniae SerRS (PDB ID 6H9X), showing the eclipsing protons and bonds; (B) Same strategy for LeuSoHA, bound to re-refined T. thermophilus LeuRS (PDB ID 2V0C), displaying the staggered protons and bonds.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-(2- & 3-(PHENYLTHIO)-1H-PYRROL-1-YL)ACETIC ACIDS AS ALDOSE REDUCTASE INHIBITORS (ARIs). A CASE OF NON-CLASSICAL BIOISOSTERISM BETWEEN SULFUR AND CARBONYL GROUPS

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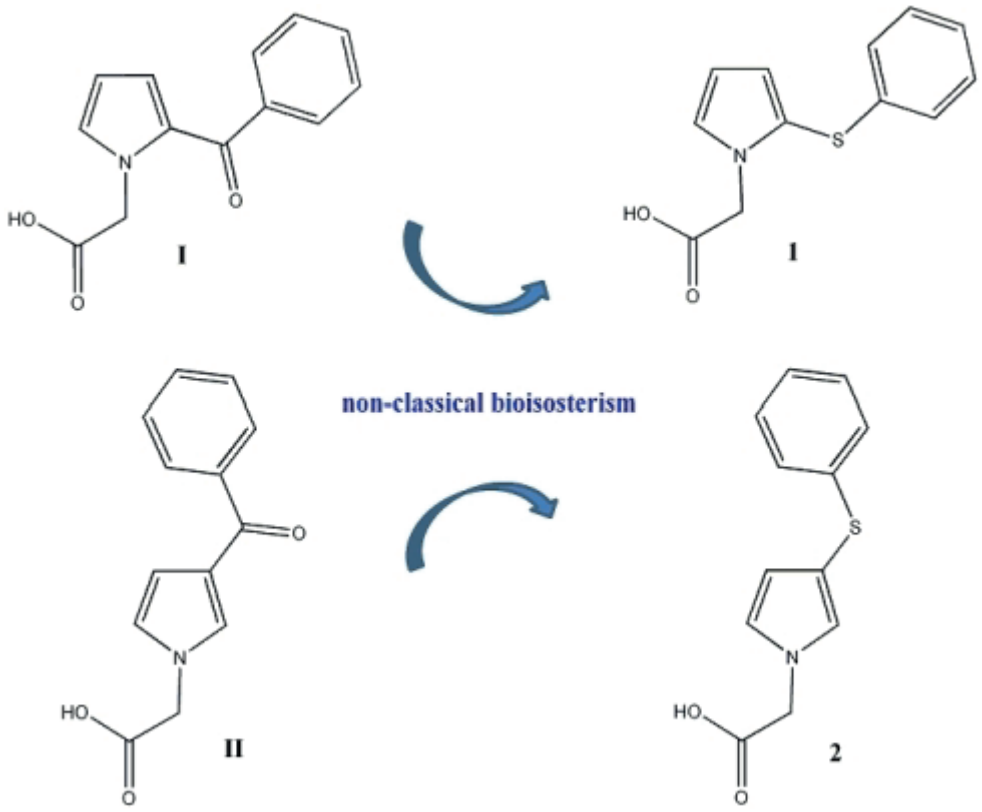
Studies show that low lying C–S σ* orbitals on S atoms, gives rise to the phenomenon referred to as σ-holes that possess positive electrostatic potential and are available for interaction with electron donating atoms, particularly N and O.[1] Thus, sulfur groups, which also feature hydrogen acceptor bonding characteristics, could be envisioned as carbonyl non-classical bioisosters. In the present study, based on the above premise, we designed the thioethers 1 and 2 as putative non-classical bioisosters to the ketones I and II, which are known aldose reductase inhibitors (ARIs).[2]



The synthesis of the target compounds involved the stepwise preparation of the appropriate isomeric pyrrolyl-thio-ethers followed by the introduction of the acetic acid moiety. *In-vitro* biological testing of 1 and 2 showed that both compounds, at low micromolar concentrations, effectively inhibited aldose reductase (ALR2). Compound 2 had similar potency as compound II, while compound 1 was a much stronger inhibitor than its keto-counterpart I. The latter improvement of activity could be the result of a more favorable low energy conformation, in combination with an increase in lipophilicity presenting hydrophobic entropic interactions with ALR2.

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SYNTHETIC CHALLENGES FOR THE DESIGN OF BIFUNCTIONAL DEGRADERS

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Proteolysis Targeting Chimeras (PROTACs) are emerging as potential therapeutics for the treatment of diseases with unmet medical needs.[1] Their structure consists of an E3 ligase inhibitor attached to a Protein of Interest (POI) binder, via a linker. PROTACs recruit together an E3 ubiquitin ligase and a target protein, forming a ternary complex, resulting in ubiquitination, and consequently degradation of the protein of interest via the ubiquitin proteasome system. This modality offers the potential to degrade disease-causing proteins previously considered undruggable. One such example are the ATPase subunits SMARCA2 and SMARCA4. In a number of cancers it has been shown that SMARCA4 lacking cells are sensitive to the loss of SMARCA2.[2] Development of efficient synthetic routes to linker conjugation and modification, allied with biochemical and structural biology techniques, has allowed the identification of ACBI1, a potent and cooperative SMARCA2 and SMARCA4 degrader that possesses anticancer activity.[3]

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NOVEL HYBRID COMPOUNDS FOR THE TREATMENT OF SKIN CANCER

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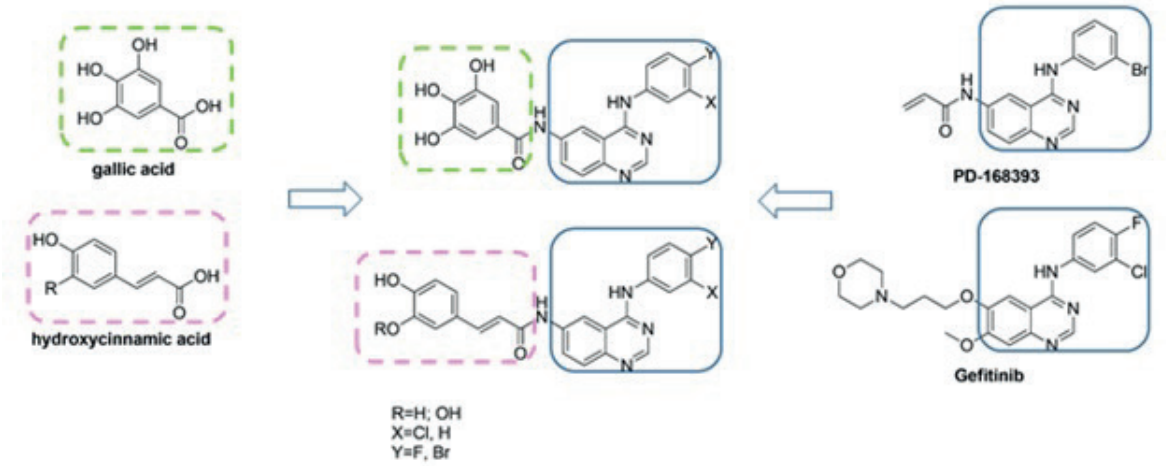
Skin cancer, which includes melanoma (CM) and non-melanoma skin cancer (NMSC), is the most common form of cancer in white population, with an incidence rate increasing worldwide.[1]

Ultraviolet (UV) radiation represents the main factor for pathogenesis of skin cancer, principally through the induction of oxidative stress due to generation of ROS, and depletion of antioxidant defense mechanisms.[2] Moreover, it has been proved that in both types of skin cancer, EGFR is often upregulated or mutated. Therefore, the inhibition of EGFR and reduction of oxidative stress could be useful targets for the treatment of skin cancer.

The objective of this study is the design, synthesis and biological evaluation of multitarget compounds with the dual profile of EGFR inhibitor and antioxidant agent. In particular, these hybrid compounds were obtained by conjugating the 4-anilinoquinazoline scaffold, that represent the typical pharmacophoric portion of EGFR inhibitors such as Gefitinib or PD 168393, with natural compounds endowed with antioxidant activity, such as hydroxycinnamic acids (caffeic acid, ferulic acid) or gallic acid.



The antiproliferative activity of these compounds was evaluated on melanoma skin cancer cells lines (501MEL) and on human squamous cell carcinoma cells (A431), a particular kind of NMSC.

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PHOTODYNAMIC INACTIVATION OF PLANKTONIC AND BIOFILM GROWING BACTERIA BY NANOMOLAR CONCENTRATIONS OF IMIDAZOLYL CATIONIC PORPHYRINS

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The worldwide emergence of multidrug-resistant (MDR) bacteria are considered by the World Health Organization (WHO) one of the main causes of mortality by infectious diseases. It has been estimated that more than 80 % of all microbial infections are caused by formation of bacteria biofilms.[1] According to WHO recommendations, an urgent investment in R&D is essential for the development of new antibacterial entities with alternative mechanisms of action, to avoid that around 10 million people will die annually worldwide by 2050.[2,3] Antimicrobial photodynamic therapy is one of the methodologies that has received significant attention, for not being associated with the development of microorganism resistance after treatment.[4] The present work intends to overcome these challenges by the development of new photosensitizers based on cationic imidazolyl moieties with different amphiphilicities, molecular weights and number of charges. Their antimicrobial activity was tested towards a panel of pathogenic microorganisms: Gram-positive *(Staphylococcus aureus)*, Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and *S.aureus* biofilms. Total inactivation was found for concentrations as low as 100 nM in planktonic bacteria with irradiation at 415 nm (LED, 1.36 J/cm^2). On the other hand, in *S.aureus* biofilm, we observed the size and number of charges effect and an irradiation with 5 J/cm² in the presence of just 5.2 nM of the smaller photosensitizer showed an impressive destruction of the biofilm (~99,43 %). Confocal images plays a very interessant role to justify this impressive results. Based on this unprecedented results, Zn(II) complexes of (1,3-dimethylimidazol-2-yl)porphyrinates open new opportunities for PDI of antibiotic-resistant bacteria and biofilms .

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SYNTHESIS OF NEW KAPPA OPIOID RECEPTOR-SELECTIVE FLUORESCENT PROBES AND APPLICATION FOR HOMODIMERIZATION STUDIES UNDER PHYSIOLOGICAL CONDITIONS VIA SINGLE MOLECULE MICROSCOPY

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G protein-coupled receptors (GPCRs) are a major class of drug targets. The four opioid receptor (OR) subtypes (μ, δ, κ and the nociception receptor subtype) located on neuronal cells represent important targets for pain management. The classic viewpoint on GPCRs functioning as single units is nowadays shifting to certain GPCRs forming oligomeric complexes with distinct pharmacology. [1]

The main goal of our project is investigating κOR homodimerization in neutral state (i.e. the non-activated state of the receptor, as bound to an G-protein and β-arrestin antagonist and not to an inverse agonist). We designed, synthesized and characterized a set of subtype-selective fluorescent ligands using the antagonist 5'GNTI (figure) linked to Cy3 and Cy5 dyes (figure) via suitable spacers (aliphatic, biglycine, tetraglycine). [2-5]

Subsequently, two of the compounds were used to study receptor localization, dynamics and potential dimerization via Single Molecule Microscopy (SMM). This technique allows individual receptor visualization on the surface of living cells. Our results do not support neutral-state κOR dimerization on the plasma membrane at physiological receptor densities.

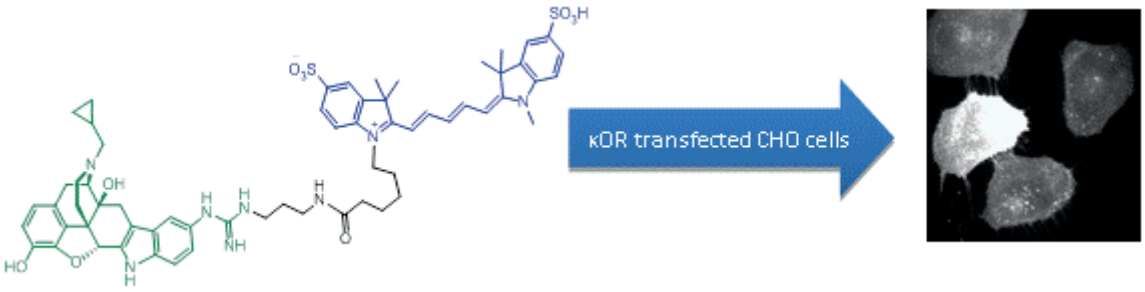

Figure: 5'GNTI (green) linked to Cy5 dye (blue) with an aliphatic spacer (black). CHO cells after overnight transfection with κOR are incubated with the probe (20 min incubation / 1 nM). High affinity κOR binding and very good optical properties are exhibited by the fluorescent probe

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INVESTIGATION OF CARBONIC ANHYDRASE ISOZYME ACTIVE CENTER CAVITIES USING BENZENSULFONAMIDES

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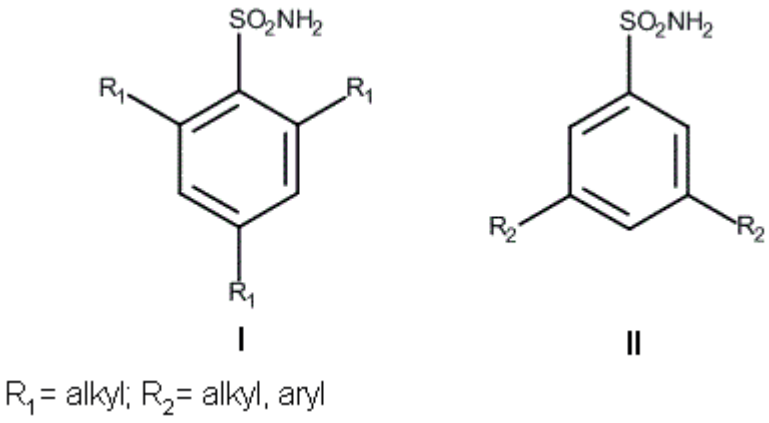
Carbonic anhydrases are involved in numerous physiological and pathological processes, including respiration and transport of CO_2/bicarbonate between metabolizing tissues and lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues/organs, biosynthetic reactions (e.g., gluconeogenesis, lipogenesis, and ureagenesis), bone resorption, calcification, tumorigenicity, and many other such processes in humans. Many of the carbonic anhydrase isozymes involved in these processes are important therapeutic targets with the potential to be inhibited or activated to treat a wide range of disorders [1]. A critical problem in the design of carbonic anhydrase inhibitors is related to the high number of isoforms, their rather diffuse localization in many tissues/organs, and the lack of isozyme selectivity of presently available inhibitors.

The main class of carbonic anhydrase inhibitors is constituted by substituted aromatic sulfonamides. We have synthesized benzensulfonamides (**I** , **II**) bearing substitutes of different size and functionality. All twelve cytoplasmic and membrane-bound carbonic anhydrase isozyme catalytic domains were cloned, expressed, and purified for biophysical studies. Inhibitor binding to the carbonic anhydrase isozymes was determined by isothermal titration calorimetry and thermal shift assay. The compounds were also computationally docked to the active sites of several carbonic anhydrases. The structural arrangement of docked inhibitors in the active site was compared to several crystal structures. The interaction thermodynamics of synthesized compounds with different carbonic anhydrase isozymes provided information about active center cavities and optimal inhibitor size thus contributing towards creating isozyme-specific inhibitors.



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DECIPHERING THE ROLE OF SPECIFIC TEAR FILM LIPIDS IN DRY EYE SYNDROME

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Dry eye syndrome (DES) is a disease of the ocular surface characterized by tear film instability, hyperosmolarity and ocular surface damage. DES has a prevalence of 10–30% in the adult population[1] and constitutes a heavy economic burden with estimated annual direct and indirect costs of $55 billion in the US alone.[2] One of the main causes of DES is thought to be an alteration in the composition of the outermost layer of the tear film, the tear film lipid layer (TFLL), resulting in increased evaporation of water from the tear film and subsequent drying of the ocular surface.[3] It was previously suggested that the specific TFLL-lipids *O*-acyl-ω-hydroxy-fatty acids (OAHFAs) and diesters (DiEs) may play a role in development of DES.[4] However, the specific connection to DES was largely unknown due to the lack of information on their biophysical properties which would shed light on their function in the TFLL.

In order to obtain insights on the role of these lipids in the TFLL, we synthesized a library of structural analogues and studied their surface behaviour at the air-water interface and the evaporation resistance of the films formed. Our results showed that only one of the previously suggested lipid classes have the desired anti-evaporative properties which are of importance in a properly functioning TFLL.[5] At the conference, the results of our recent studies on the topic will be presented.

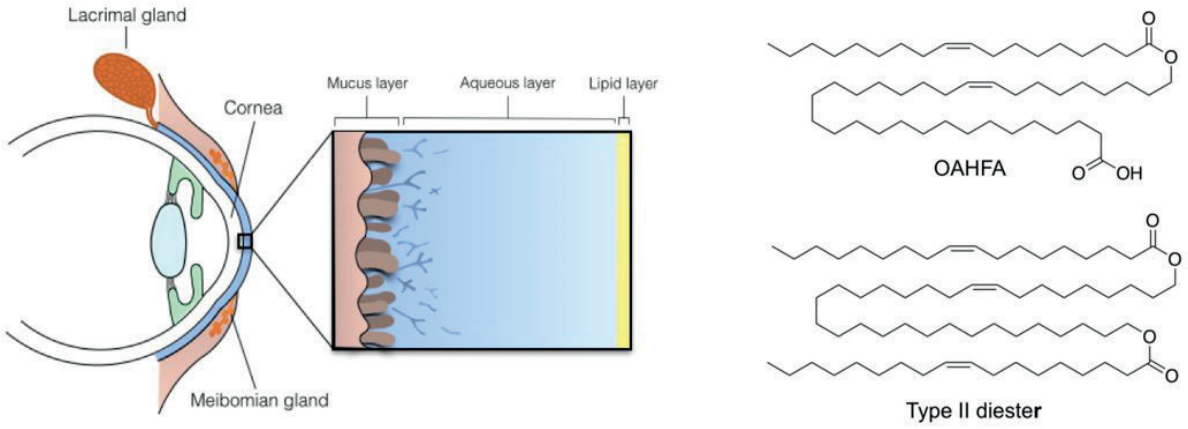

Figure 1. **Left:** Schematic view of the eye, highlighting the tear film. **Right:** Special lipid classes found within the TFLL.

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PHARMACOPHORIC STUDIES OF COUMARINS FROM HAPLOPPAPUS MULTIFOLIUS AS CYCLOOXYGENASE 2 INHIBITORS

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Coumarins are widely distributed in plants, bacteria and fungi, their multiple biological properties and low toxicity have transformed them into an interesting field of study for new drugs of natural origin. *Haplopappus multifolius* Phil. is an endemic Asteraceae [1] distributed in pre-Andean zones of Central Chile. It belongs to "Bailahuén Complex" that groups seventeen medicinal Haplopappus species [2]. Infusions of resinous leaves of shrubs are traditionally used in relief of liver, respiratory, intestinal and urinary ailments [3], as well as topic antiseptic for wounds treatment [4]. COX-2 is a key enzyme in carcinogenesis and inflammation and some natural and synthetic coumarins have been probed as COX-2 inhibitors [5-7].

In this work, we assayed 8 coumarin isolated from ethanolic extracts of *Haplopappus multifolius* [8-9], by measuring their IC_{50} values as *in vitro* inhibitors of COX-2 by a commercially avalaible kit, using quercitine as positive control [10]. The best inhibitor was 7-hidroxycoumarin (Umberliferone).

Computational studies including energy optimization with MMFF94x forcefield and low energy conformers generation were done on MOE 2009 for the 8 compouds. QSAR were performed using GA-MLR and AutoQSAR MOE-MLR. The flexible alignment and consensus pharmacophore were obtained using an unified scheme.

The pharmacophore analysis of the compounds showed that the common structural features presented in the compounds are the presence of one group acceptor of hydrogenbonds attached to two aromatic/hydrophobic moieties with a rigid structure and electrons on p orbitals in the conjugated ring. The best QSAR models for the enzyme inhibition were obtained using GA-MLR and this data will be used for virtual screening.

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N-ALKYL L-IMINOSUGARS AS NOVEL ANTI-INFLAMMATORY AND ANTI-BIOFILM TOOLS FOR CYSTIC FIBROSIS LUNG INFECTIONS

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Chronic inflammation of airways and polymicrobial infections greatly contribute to the irreversible lung damage in Cystic Fibrosis (CF) disease.[1] Accordingly, increasing attention is currently devoted to development of novel anti-inflammatory as well as antibiofilm agents for the treatment of CF lung infections. In this context, D-iminosugars (sugar analogues with an amino function in place of the endocyclic oxygen) have recently shown interesting *in vitro* and *in vivo* anti-inflammatory effect, by targeting β-glucosidase 2 (NLGase).[2] However, as widely reported, the poor *in vivo* selectivity of D-iminosugars hampers their long-term use as therapeutics.[3] Conversely, their non-superimposable mirror images, L-iminosugars, have shown higher selectivity than their D-counterparts toward specific enzymes acting as either inhibitors or enhancers.[3,4] Based on these findings, in order to explore role of iminosugar configuration on the therapeutic potential of these molecules in the treatment of CF lung infections, we tuned up a novel synthetic procedure for the preparation of L-DNJ, i.e. L-deoxynojirimycin, and its *N*-alkylated derivatives (**Figure 1**).

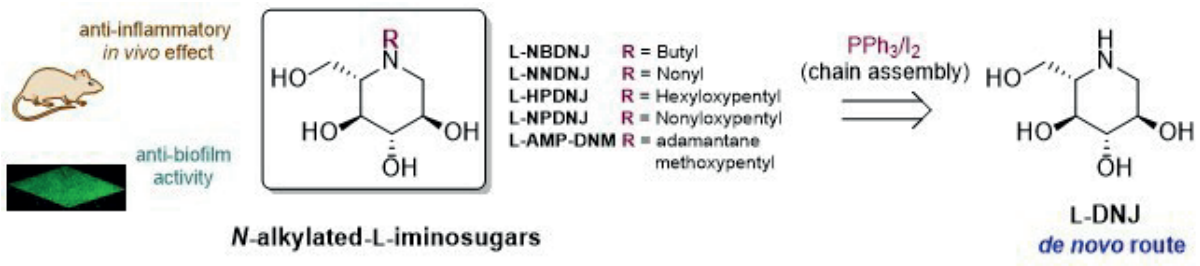

Figure 1 *De novo* route to L-DNJ and its *N*-alkyl derivatives.

Particularly, access to the iminosugar core has been devised through a stereocontrolled *de novo* procedure,[4] while the use of polymer-bound triphenylphosphine/iodine complex has been conceived for the assembly of the alkyl chains. Biological assays for some derivatives revealed, on one hand, an anti-inflammatory activity in CF bronchial cells as well as in murine models of lung infection, on the other, promising antibiofilm activity against some pathogens involved in chronic lung infections characterizing CF patients.

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TARGETING A BEST-IN-CLASS PROFILE: THE IDENTIFICATION OF NVP-CLR457 AS A NON-CNS-PENETRANT PAN-CLASS 1A PHOSPHOINOSITOL-3-KINASE INHIBITOR

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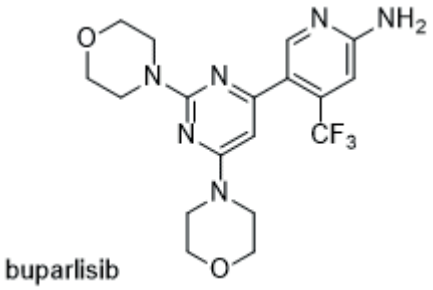
A number of isoform selective and pan-phosphoinositol-3-kinase (PI3K) inhibitors are currently undergoing clinical trials for the treatment of a range of cancers. One key question is which combination of PI3K and additional lipid kinase activities can be administered with acceptable clinical safety to deliver the optimal treatment for each indication. The inhibition of certain PI3K isoform(s) has been linked to different malignancies, including: dysregulation of PI3Kα in breast, ovarian, colon and brain; PI3Kβ in tumors with defficiencies in PTEN function; and PI3Kδ in some hematologic malignancies.[1] Included in the compounds currently studied in the clinic is buparlisib (NVP-BKM120), a class 1A pan-PI3K inhibitor identified within Novartis.[2] Although buparlisib is showing encouraging clinical data, opportunities to further improve upon the profile of the compound were identified with the aim of delivering a best-in-class pan-PI3K inhibitor. The three main areas targeted for improvement over buparlisib were: 1) to better equilibrate, and to improve, the potencies across the class 1A PI3K isoforms; 2) to eliminate the tubulin binding that mediates the compounds off-target activity;[3] 3) to minimise PI3K inhibition within the CNS to improve the safety profile.

Taking the buparlisib chemical series as the starting point, we will describe the successful optimisation of the scaffold to deliver the above targeted profile, culminating in the identification of the clinical candidate NVP-CLR457.[4]



buparlisib

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SYNTHESIS OF HOMODIMERS BASED ON 1,4-NAPHTHOQUINONE AS GENERATORS OF REACTIVE OXYGEN SPECIES

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It is well known that compounds which have a quinone nucleus on their structure, exhibit diverse biological activities, such as antifungal, antimaralial, and antitumour. regarding this last one, the therapeutic effect could be held by three mechanisms: 1) bioreductive alkylation, 2) DNA intercalation and 3) redox cycling[1]. since quinones are easy to be reduced, redox cycling is considered the main mechanism. In this framework, 1,4-naphthoquinones are considered as privileged structure for the synthesis of antineoplastic agents, since it is easy to generate reactive oxygen species; which are increased when chlorine, hydroxy, and amino groups, are present on the structure[2–4].

On the other hand, the twin-drug approach is a strategy used in medicinal chemistry, with the purpose to obtain a new compound which has two pharmacophoric entities in one, to generate a more potent and/or selective drug[5]. So, with the aim to obtain new homodimers which act as redox cyclers, they have been synthesized new homodimers and their respective monoamination compound based on 1,4-naphthoquinones with aromatic and aliphatic amines, by one-pot synthesis. The novel derivatives will be test as ROS generators on *Staphylococcus aureus*. In order to make a SAR study, the chain length, substituents, and the change from aromatics to aliphatics have been proposed. Additionally, it could be possible, the comparison between the monoamination compound and the respective homodimer; It is expected, that homodimers, which have two quinonic nuclei on their structure generate more reactive oxygen species than the monoamination compound, which have just one quinonic nucleus. This study would be a preliminary study for intracellular ROS generation.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF QUATERNARY AMMONIUM FLUOROQUINOLONES

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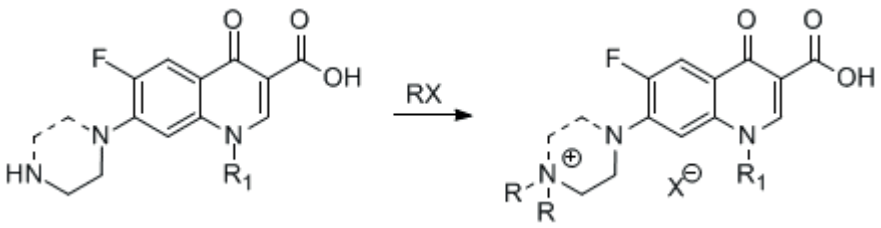
Fluoroquinolones are broad-spectrum antibiotics (effective for both gram-negative and gram-positive bacteria) that play an important role in the treatment of serious bacterial infections, especially hospital-acquired infections and others in which resistance to older antibacterial classes is suspected. Since the discovery of nalidixic acid by George Lesher in 1962 over ten thousand analogues have been synthesized from which four generations of chemotherapeutics with a broad spectrum of antibacterial activities have emerged.

Safirinium dyes are water-soluble and inexpensive fluorophores that possess triazolo-pyridinium core (1-2). Recently we have synthesized a series of fluorescent *Safirinium*-fluoroquinolone hybrid compounds featuring fused quaternary quinolone-triazolinium moiety that exhibited biological effects. Novel derivatives showed a pronounced in vitro antibacterial and antibiofilm activity against various pathogens, including *Pseudomonas aeruginosa*. The obtained conjugates were potent *E. coli* DNA gyrase inhibitors and caused a defect in DNA decatenation. The most active compounds were found to be comparable to the reference drug, ciprofloxacin (unpublished results). Moreover, the presence of quaternary nitrogen atom in the structure should prevent distribution to the brain (3) and such hybrid agents should not elicit the direct CNS side effects after intravenous administration.

In view of the above, we have synthesized a series of quaternary analogues of fluoroquinolones with dimethylpiperazinium moiety. Antibiofilm activity of obtained compounds was investigated. Molecular docking experiments were undertaken to confirm the mode of action of the novel antibacterials.



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DESIGN, SYNTHESIS AND ANTITUMOR EVALUATION OF STEROIDAL OXIMES AND EPOXIDES

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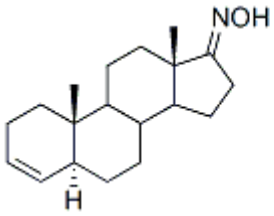
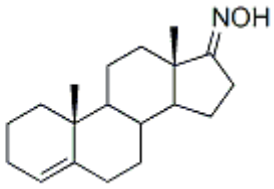
Cancer is a worldwide disease, causing numerous deaths every year. The metabolism of cancer cells is altered compared to the normal ones, leading to an abnormal cellular growth, which enables them to metastasize to other organs. Currently, several strategies are used to help fight cancer among them the use of antitumor chemotherapy. Steroidal compounds were proven to be efficient against several types of cancer. Epoxides and oximes are also two structural features frequently associated with anticancer activity. In this manner, it was our intention to combine these features with the steroidal backbone by synthesizing steroidal epoxides and oximes and evaluating them in several cancer cell lines, ultimately to find new anticancer agents with fewer side effects. The compounds 5α-androst-3-en-17-one oxime (**3,4 – OLOX**), 3α,4α-epoxy-5α-androstan-17-one oxime (**3,4 – EPOX**), androst-4-en-17-one oxime (**4,5 – OLOX**) and 4α,5α-epoxyandrostan-17-one oxime (**4,5 – EPOX**) were synthesized and their cytotoxicity evaluated in four human cancer cell lines, namely, colorectal adenocarcinoma (WiDr), non-small lung cancer (H1299), prostate cancer (PC3) and liver hepatocellular carcinoma (HepG2) cell lines. In this study, we used the MTT assay to assess the cytotoxicity of the compounds with a concentration ranging from 1 to 75 μM. The most effective compound in the antiproliferative studies in all the cell lines studied was **3,4 – OLOX**. Furthermore, WiDr and PC3 demonstrated the best IC_{50} results (9.1 μM and 13.8 μM, respectively). **4,5 – OLOX** also showed promising results in the same cell lines with an IC_{50} of 14.5 μM in PC3 and 16.1 μM in WiDr cell lines. The compounds with an epoxide function in the steroidal A-ring did not show any differences comparing to the control in all cell lines. On the contrary, compounds with a double bond in the referred A-ring were quite active, showing that this functional group seems to be important for the cytotoxicity observed. The oxime function, in some compounds, appears to have a role in the antiproliferative activity. Preliminary results suggest that two of the synthesized compounds (**3,4 – OLOX** and **4,5 – OLOX**) might have an antitumoral effect which encourages further studies.





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DISCOVERY OF MRK-740, A FIRST-IN-CLASS, POTENT, SELECTIVE AND CELL ACTIVE PRDM9 INHIBITOR

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PRDM9 is a PR domain containing protein which trimethylates histone 3 on lysine 4 and 36. Its normal expression is restricted to germ cells and attenuation of its activity results in altered meiotic gene transcription, impairment of double-stranded breaks and pairing between homologous chromosomes. There is growing evidence for a role of aberrant expression of PRDM9 in oncogenesis and genome instability. In this poster we report our screening, hit finding and lead optimization efforts leading to the discovery of MRK-740, a first-in-class, potent (IC_{50}: 85 ± 17 nM), selective and cell active PRDM9 inhibitor. MRK-740 binds in the substrate-binding pocket, with unusually extensive interactions with the cofactor S-adenosylmethionine (SAM), conferring SAM-dependent substrate competitive inhibition. MRK-740 is the first chemical probe for the PRDM subfamily of methyltransferases and highlights the potential for exploiting SAM in targeting SAM-dependent methyltransferases.

RADICAL ARYLATION IN THE SYNTHESIS OF HIGH-AFFINITY AND HIGHLY SUBTYPE-SELECTIVE M3 RECEPTOR LIGANDS

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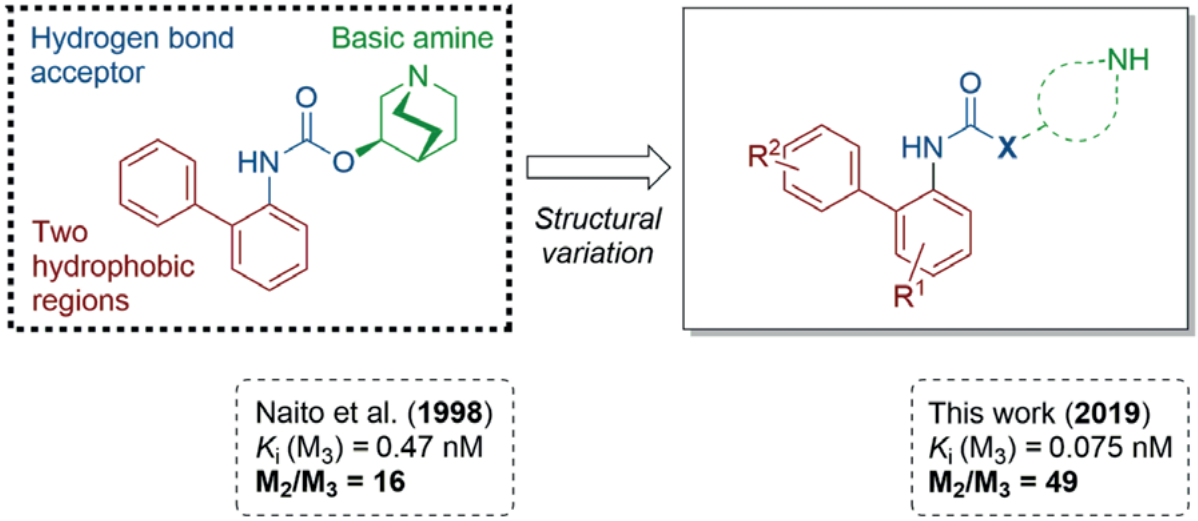
Recently developed synthetic methods for the synthesis of 2-aminobiphenyls[1-3] were applied in the structural optimization of M_3 subtype-selective muscarinic receptor ligands. These methods take advantage of a radical arylation procedure using cheap starting materials without the need for expensive catalysts. Variations on the two aromatic cores and the basic alkylamine moiety led to a strong increase of binding affinity and remarkable subtype-selectivity[4] compared to previously published M_3 antagonists bearing a biphenyl motif.[5]



Even though the M_3 receptor subtype is known to be the main mediator of bronchoconstriction in *in-vivo* studies, current anti-muscarinic drugs, such as tiotropium bromide, do not show significant subtype-selectivity.[6] Despite the fact that tiotropium bromide shows a certain 'kinetic selectivity' towards M_3 resulting from an elevated residence time at the receptor, inhibition of M_2 autoreceptors caused by tiotropium bromide provides feedback which increases ACh release and therefore bronchoconstriction.[7] Additionally, due to its cross-activity, the therapeutic dose is limited by the increased risk of cardiovascular events, which is of particular importance for inhaled tiotropium bromide where higher peak concentrations can be observed.[8] Against this background, there is a demand for novel subtype-selective M_3 receptor antagonists, which are subject to current research.

The newly developed ligand shows binding affinity to the M_3 subtype in the low picomloar range with a 49-fold selectivity for M_3 over M_2, which puts it among the top high-affinity M_3 subtype-selective ligands[9], but exceeds them by its facile synthesis.

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A NOVEL SYNTHESIS OF INDOLE-2-CARBALDEHYDES AS BUILDING BLOCKS FOR BIOLOGICALLY ACTIVE COMPOUNDS

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The indole ring is the parent heterocyclic scaffold of numerous drugs and bioactive compounds [1,2]. Many of these bioactive indoles are substituted at the 3-position. While for instance indole-3-carbaldehydes were claimed as a class of antimitotic agents with anticancer activity [3], less attention has been devoted to synthesis and properties of indole-2-carbaldehydes. We were interested in these structures as versatile building blocks in the course of a project towards potential inhibitors of DYRK kinases [4,5]. We here announce a novel synthesis procedure for indole-2-carbaldehydes which involves oxidative degradation of 2-allylindoles employing Lemieux-Johnson conditions. The reaction sequence may be performed as one-pot process. Yields and scope of the new reaction will be reported in the presentation.

Acknowledgements:

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TRICKS OR TREATS: ORGANORUTHENIUM(II) GLYCOCONJUGATES AS ANTICANCER AGENTS

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Hypoxic cancer cells rely on energetically inefficient aerobic glycolysis, overexpressing glycolytic proteins to comply with high proliferation rates (Warburg effect) [1]. Glucose Transporter 1 (GLUT1) is overexpressed in many human cancers, with levels correlating with cancer invasiveness, metastatic potential, and poor survival prognosis [2,3]. Hexokinase II (HKII) is also overexpressed in Warburg-phenotype tumours, being responsible for glucose phosphorylation to G6P upon GLUT1 uptake[4]. Glycoconjugation of a cytotoxic agent thus affords a tumour selectivity vector, tackling GLUT1 uptake for selective delivery of cytotoxic payloads at CC/PC tissues and HKII inhibition/metabolization for anticancer effect.

Known for high cytotoxicity and low general toxicity, Ru compounds are the most studied and promising among non-platinum chemotherapeutic alternatives[5]. Our effort to build lybraries of ruthenium(II) glycoconjugates [6] recently led to the first GLUT-uptaken ruthenium(II) glycoconjugates, a milestone in Ru anticancer research [7] (Figure 1). In this communication we disclose newly designed cyclopentadienylruthenium(II) glycoconjugates (Figure 1).

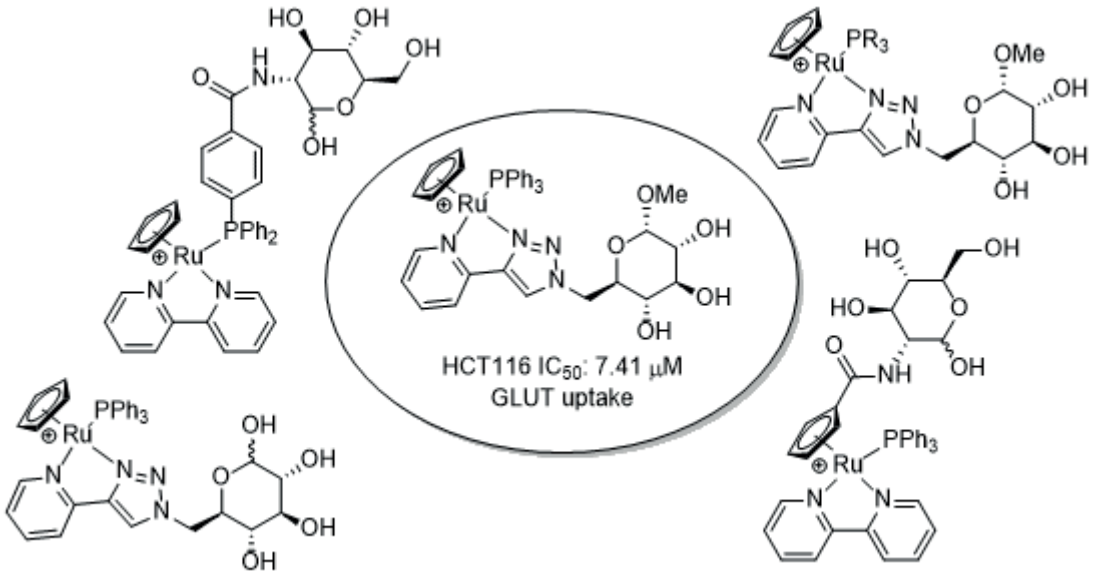

Figure 1

Cytotoxicity (IC50) of organoruthenium(II) glycoconjugates is evaluated in colon (HCT116) and pancreas (MiaPaCa-2) cancer cells, and primary human hepatocytes for selectivity evaluation. GLUT1 uptake and HKII inhibition abilities are studied by biochemical methods and correlated with *in silico* data (docking).

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NEW NIFURTIMOX-ADAMANTANE HYDRAZONE ADDUCTS: DESIGN, SYNTHESIS AND EVALUATION OF TRYPANOCIDAL ACTIVITY

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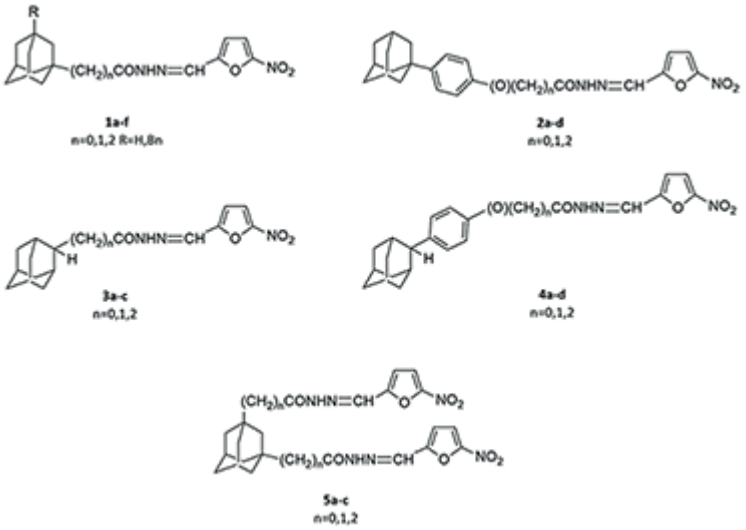
Five to eight million people in Latin America are infected with the protozoan parasite Trypanosoma cruzi, the aetiologic agent of Chagas disease. Although the disease occurs mainly in Latin America, migration and travel have extended the distribution to other continents including North America, Europe and parts of the Western Pacific, where significant numbers of Chagas disease sufferers can now be found. The current drugs, benznidazole and nifurtimox, are characterized by limited efficacy and toxic side-effects, and treatment failures are frequently observed. This has led the World Health Organization (WHO) to coordinate public sector and private partnerships as part of a global effort to develop new and safer drugs.

Over the past 10 years we have been interested in adamantane chemistry and have prepared numerous adamantane derivatives with antitrypanosomal potency [1-2], exploiting adamantane's role in bioactivity. Herein, the synthesis and pharmacological evaluation of the C-1 substituted adamantane hydrazones **1a-f**, **2a-d**, C-2 substituted hydrazones **3a-c**, **4a-d** and the C-1,3 1,3-disubstituted derivatives **5a-c** is described [3-4].

The nifurtimox-adamantane hydrazone adducts are more potent trypanocidals than the parent drug, nifurtimox. The effect of the presence of the phenyl ring, in conjugation with the hydrazone side chain, on activity, shows an adamantane position substitution dependence. The insertion of a phenyl ring between the adamantane core and the hydrazone side chain has improved the pharmacological profile, in terms of activity and toxicity. The most active adduct with the best selectivity is the phenylacetoxy hydrazone **2b** (EC_{50}=11 ± 0.9 nM and SI_{Tb}=770).



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CAPTURING AND APPLYING KNOWLEDGE TO GUIDE COMPOUND OPTIMISATION

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Compound design requires a combination of knowledge and expertise from different perspectives: Understanding of structure-activity relationships (SAR), based on data from previously studied compounds; expertise from diverse fields to define the multi-parameter optimisation (MPO) objectives of a project; and knowledge of synthetic strategies that may be applicable to create the next rounds of compounds for investigation. All of these forms of knowledge can be captured and applied computationally: Machine learning methods can generate quantitative structure-activity relationship (QSAR) models to predict the properties of novel, virtual compounds; MPO methods capture the desired property criteria for a successful compound for a specific project and rigorously prioritise ideas for consideration; and, optimisation strategies can be captured as structural transformations that reflect steps made in previous chemistry projects.

In this presentation, we will describe these methods and illustrate how they can be seamlessly combined to rigorously explore new, relevant compound ideas and prioritise those most likely to achieve a project objective. This approach can help to stimulate the search for new optimisation strategies and explore a much broader range of compounds than could be achieved based on a single chemist's or even a project team's experience. Example applications include the optimisation of compounds with a desired polypharmacology or selectivity profile and exploration of lead hopping strategies to overcome pharmacokinetic issues, while maintaining target potency.

DESIGN AND SYNTHESIS OF NOVEL BIOINSPIRED HYBRID COMPOUNDS AS PROTEASOME ACTIVATORS WITH ANTI-AGING ACTIVITY

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The proteasome constitutes one of the vital cellular proteolytic machineries that maintain protein homeostasis (proteostasis) and participates in almost all cellular functions through the degradation of misfolded, redundant, and damaged proteins. Proteasome has been reported to decline in terms of quantity and function during aging and age-related diseases progression[1]. Thus, proteasome activation constitutes a central mechanism for the deceleration of organismal aging and of the progression of neurodegenerative diseases such as Alzheimer's and Huntington's diseases, which are related with accumulation of toxic protein aggregates[1]. Research towards the discovery of drug-like proteasome activators is a relatively unexplored field at an infant stage[2].

In the context of the present study, novel hybrid compounds, combining the structural features of the natural antioxidant vitamin E and of hydroxytyrosol, which is the main polyphenolic constituent of olive oil with a variety of biological properties, in one scaffold, were designed and synthesized. It is noteworthy that vitamin-E, its water soluble analog trolox, as well as hydroxytyrosol do not exhibit proteasome activating properties *per se*.

The new analogues were evaluated for their ability to activate the proteasome in human primary fibroblasts *in cellulo* as well in the test tube using highly purified 20S proteasome. The identified activators were administered to the cells throughout their replicative lifespan revealing an extending effect. Their anti-aging properties were further tested in the multicellular level, using the aging model, namely the nematode *Caenorhabditis elegans*. Our data identified very promising anti-aging agents with the ability to extend cellular and organismal lifespan[3].

Acknowledgements: This research has been co-financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH – CREATE – INNOVATE (project code: T1EDK-01610). This work was also supported by the project “STHENOS-b" (MIS 5002398), funded by the Operational Programme "Competitiveness, Entrepreneurship and Innovation" (NSRF 2014-2020) and co-financed by Greece and the EU (European Regional Development Fund).

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DISCOVERY OF SMALL MOLECULE INHIBITORS OF FASCIN 1 USING FRAGMENT-BASED DISCOVERY

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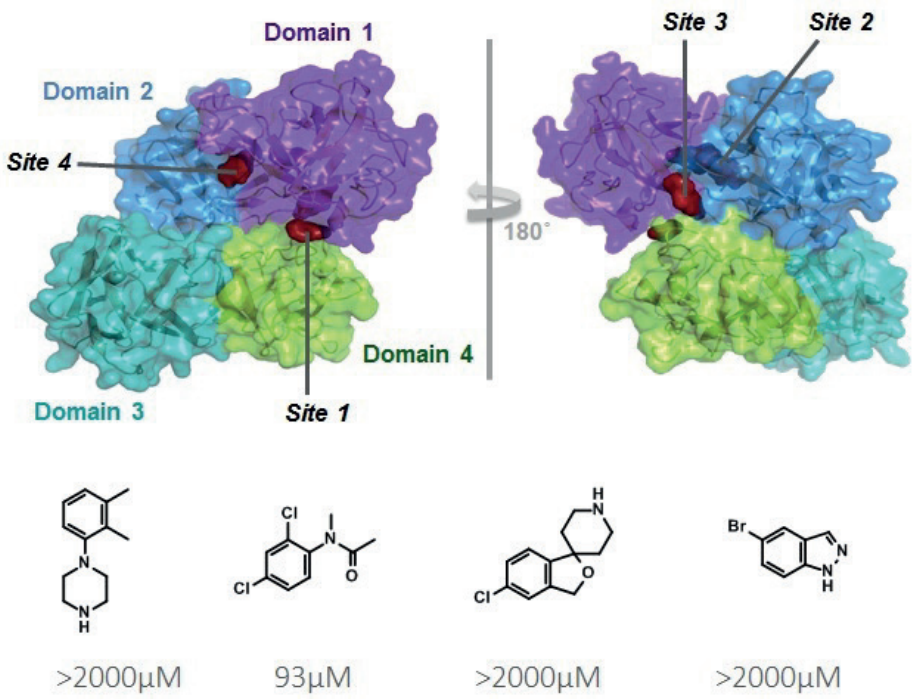
Fascin 1 binds and cross-links filamentous actin (F-actin) into parallel bundles that are used in the formation of dynamic cellular protrusions (such as lamellipodia and filopodia) during cell migration, and in the formation of invadopodia used by tumor cell lines to degrade the tumor extracellular matrix (ECM). Fascin 1 is overexpressed in a range of aggressive and invasive tumors and is believed to play a critical role in cancer cell metastasis. Utilising our in-house fragment collection (~1000 compounds) coupled with biophysical assays and X-ray crystallography, we identified novel fascin 1 inhibitors binding in multiple ligand binding sites the best of which show nanomolar affinity in biochemical binding and bundling assays. We will show several series of compounds binding with high affinity whilst demonstrating functional activity of which our best-in-series compound includes BDP-00013176 (K_d=85nM, IC_{50}=240nM). These lead compounds have now been tested in a number of cell based invasion assays including both 2D and 3D cultures, demonstrating the potential of fascin inhibition as a valid target for preventing tumour invasion and metastasis.



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PHOSPHORUS FUNCTIONALITIES AS NOVEL OPTIONS FOR STRUCTURAL DEVELOPMENT: PROPERTIES AND ESTROGENIC ACTIVITY OF 4-PHOSPHINOPHENOL DERIVATIVES

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Expanding the chemical space of biologically active compounds is a promising strategy to develop novel and distinctive drug candidates, and the application of organic multi-elemental compounds is a reasonable approach to increase the options for structural development. We have been investigating the incorporation of inorganic and organometallic functionalities in biologically active compounds, and previously reported the development of boron cluster-based compounds [1] and silicon/germanium-containing derivatives [2]. In this study, next we focused on phosphorus-containing functionalities as the novel options for structural development. Using the 4-phosphinophenol substructure as a common platform, we designed and synthesized a series of phosphorus-containing compounds including phosphine oxide, phosphine sulfide and phosphine borane, and systematically evaluated the physicochemical properties such as hydrophobicity of the compounds and acidity of the phenolic hydroxyl group (Figure 1). The hydrophobicity of compounds was determined in terms of hydrophobicity parameter LogP by the HPLC method. The larger LogP values were given in the order of phosphine, phosphine borane (BH_3), phosphine sulfide, and phosphine oxide. Phosphine borane trihalide exhibited the larger LogP values than that of the corresponding BH_3 phosphine borane derivative. The acidity of the compounds was determined in terms of acid dissociation constants (pK_a values) by the pH-dependent absorption spectra. We found that the larger pK_a values were also given in the order of phosphine, phosphine borane (BH_3), phosphine sulfide, and phosphine oxide. Phosphine boranes including trihalides exhibited the electron-withdrawing character in compare to the corresponding phosphine. Since the 4-substituted phenol is the pharmacophore of estrogen receptor (ER) ligands, we next investigated the biological activity of the phosphinophenol derivatives toward ER. Some of the compounds showed ligand potency toward ER, and interestingly, the phosphine borane derivatives exhibited potent ER antagonistic activity. Phosphine borane can be a novel and unique option for structural development of drug candidates. The synthesis of the phosphinophenol derivatives, physicochemical properties, and structure-activity relationship of ER activity including the comparison with the related alkane/silane derivatives will be reported in detail.

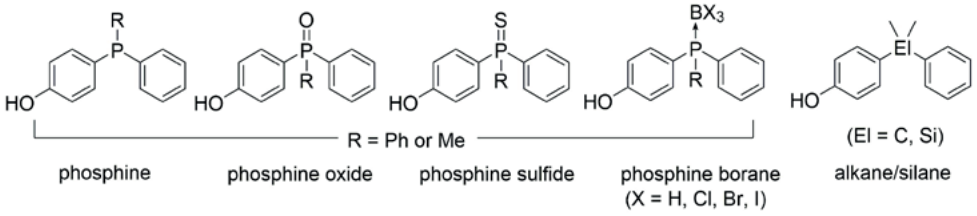

Figure 1. Structures of the synthesized phosphinophenols and related derivatives.

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DS79182026: A POTENT ORALLY ACTIVE HEPCIDIN PRODUCTION INHIBITOR FOR ANEMIA OF CHRONIC DISEASE

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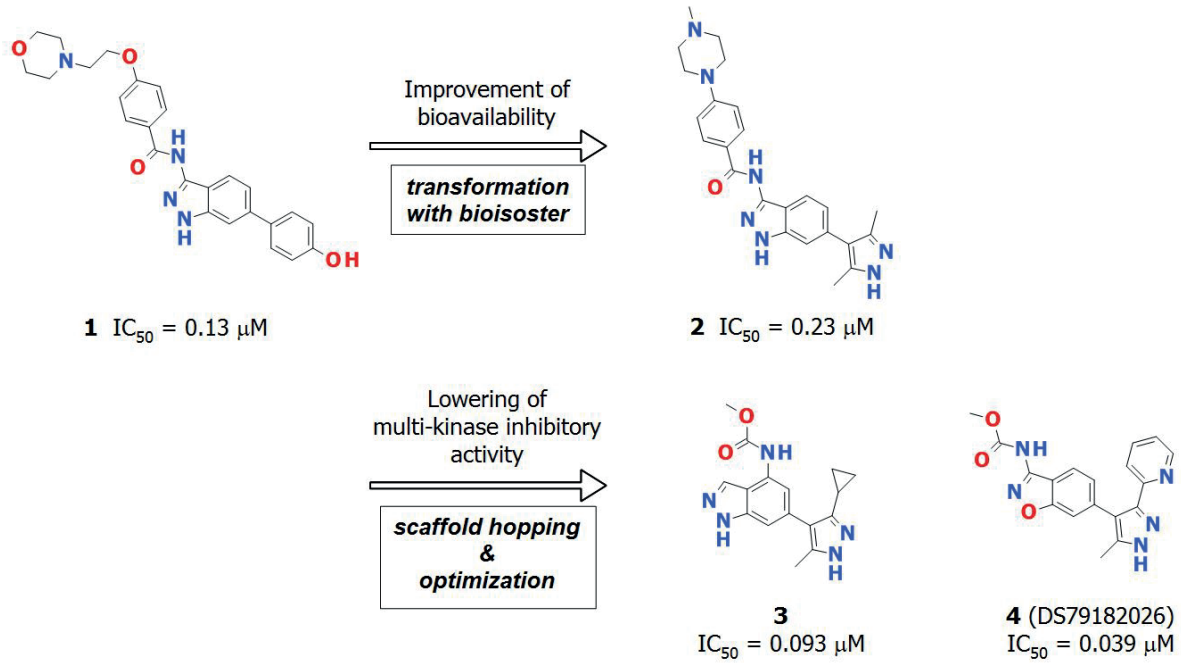
The hepatic peptide hormone Hepcidin plays an essential role in regulating dietary iron absorption, plasma iron concentration and tissue iron distribution in the body. Anemia of chronic disease (ACD), which includes anemia of inflammation, is a heterogenic anemic condition due to chronic inflammation from a basic disease, such as rheumatoid arthritis. Some ACD patients are known to present iron deficiency despite abundant body iron store (termed *functional iron deficiency*).

Recently, high hepcidin induction based on inflammatory status was recognized as the cause of functional iron deficiency. The controlling of hepcidin level would be a promising therapeutic strategy for treating hepcidin caused functional iron deficiency.

We report herein the lead optimization from **1** to obtain an indazole derivative **2**, a potent orally hepcidin production inhibitor. In addition, we describe the derivatization aimed at the lowering of multi kinase inhibitory activity of **2** to discover a potent 4-indazole derivative **3** and benzisoxazole derivative **4** (DS79182026), which showed reticulocyte hemoglobin content (CHr) recovering effects in iron-induced mouse anemia model.[1]



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HYDROGEL SCAFFOLDS WITH ACTIVE SEQUENCES AS PRO-REGENERATING FACTORS

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An indispensable condition for tissue regeneration is the presence of three-dimensional support in the form of a natural scaffold or its artificial substitute. Peptide hydrogels are very promising group of natural, self-assembling nanomaterials[1]. They can undergo spontaneous assembly into well-ordered nanofibers and scaffolds with 10nm in fibre diameter, pores between 5-200nm and over 90% of water content [2]. These peptide scaffolds have 3D nanofiber structures similar to the natural extracellular matrix (e.g. collagen). Due to their ease of modification, biocompatibility, good bioadhesive and transport properties, they offer novel therapeutic possibilities with broad potential impact on biomedicine [3].

Over the past few years, the number of peptide hydrogels with attached motifs promoting specific cellular responses has increased significantly. There are many peptide hydrogels containing sequences increasing cell adhesion and proliferation. The best characterized peptide hydrogels are RADA 16-I (Ac-RADARADARADARADA-NH_2) and RADA16-II (Ac-RARADADARARADADA-NH_2). These peptides form stable β-sheet structure in aqueous solutions. Their characteristic feature is the presence of hydrophobic and hydrophilic surfaces and creating organized supramolecular structures. These supramolecular structures are stable over a wide range of temperatures and denaturing agents.

The aim of the research was to design and synthesise new functionalized hydrogels, which sequence consist of commercially available RADA16-I, enzyme specific cleavage site and biologically activeamino acid sequence (Fig.1).

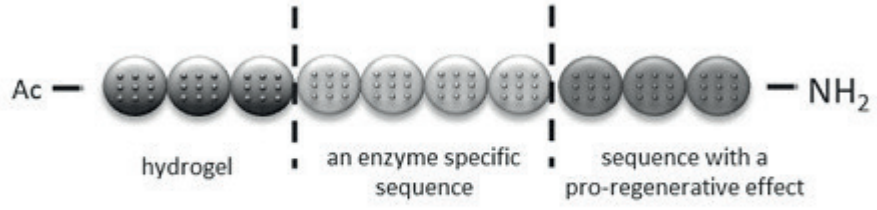

Fig.1 Schematic construct of designed hydrogel formulations.

ACKNOWLEDEGEMENTS:

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1,2-DIHYDRO-2-OXO-PYRIDINE-3-CARBOXAMIDE DERIVATIVE AS MULTI-TARGET MODULATOR OF ENDOCANNABINOID SYSTEM FOR AN INNOVATIVE THERAPEUTIC APPROACH IN MULTIPLE SCLEROSIS

Francesca Gado (1), Simone Bertini (1), Maria Digiacomo (1), Serena Meini (1), Ines Reynoso-Moreno (2), Laura Micheli (3), Paola Nieri (1,4), Erika Vallini (2), Sara Carpi (1), Beatrice Polini (1), Chiara Cervetto (4,5), Marco Macchia (1), Jürg Gertsch (2), Manuela Marcoli (4,5), Carla Ghelardini (3), Lorenzo Di Cesare Mannelli (3), Andrea Chicca (2), Clementina Manera (1,4)

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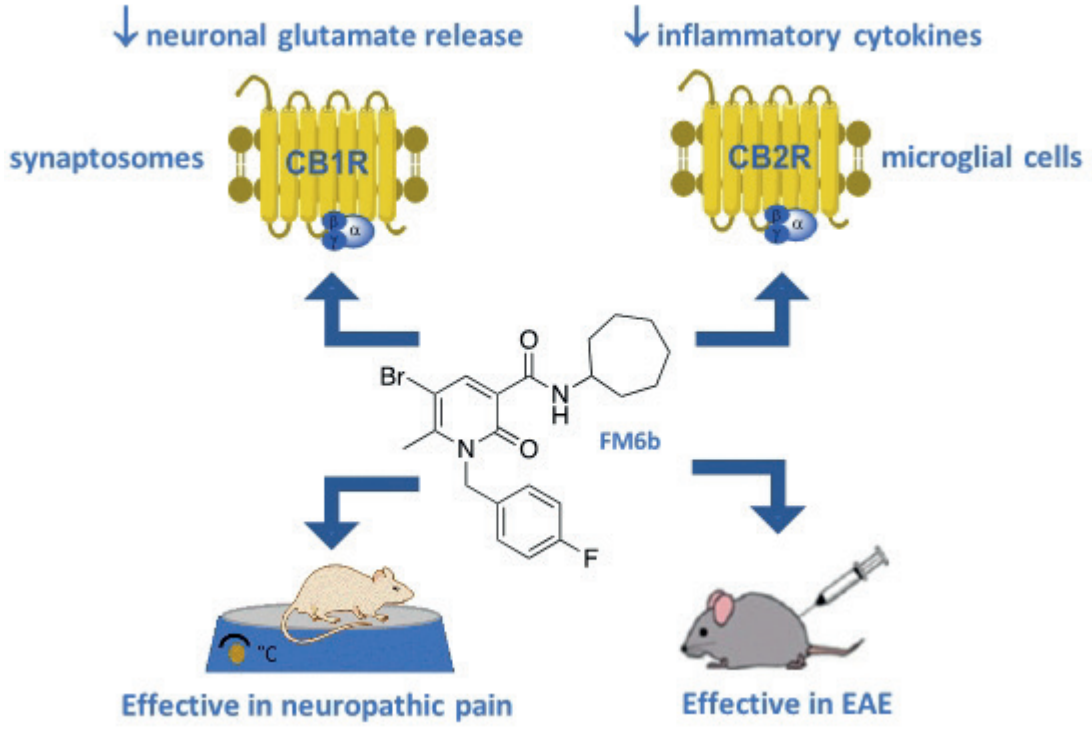
Recent findings highlight the emerging role of each target of the endocannabinoid system (cannabinoid receptors, degrading enzymes and AEA transporter) in the control of symptoms and disease progression in multiple sclerosis. From these data, it is reasonable to assume that the simultaneous modulation of more targets within this system should offer a safer and more effective pharmacological strategy as compared to the single target modulation. In a research program aimed at obtaining CBRs ligands, a series of 2-oxo-1,2-dihydropyridine-3-carboxamide derivatives variously substituted on central nucleus were synthesized. From these studies we selected the novel multi-target modulator **FM6b** that exerts "pro-cannabinoid" activities by acting with different mechanisms of action and it is characterized by good drug-like. **FM6b** was investigated *in vitro* to verify its potential to modulate the production of pro- and anti-inflammatory cytokines in activated mouse BV2 microglial cells and to evaluate its potential neuroprotective effects by limiting neuronal glutamate release, using isolated nerve terminals (synaptosomes) in superfusion system. Subsequently, the same compound was tested *in vivo* to evaluate its efficacy on the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis in mice and to assess its antinociceptive effect in an animal model of neuropathic pain.



The obtained results show that the novel multi-target modulator **FM6b** represents a promising molecule to control the symptoms and disease progression in multiple sclerosis.

DESIGN AND SYNTHESIS OF NOVEL 1,10-PHENANTHROLINE TELOMERIC G-QUADRUPLEX LIGANDS

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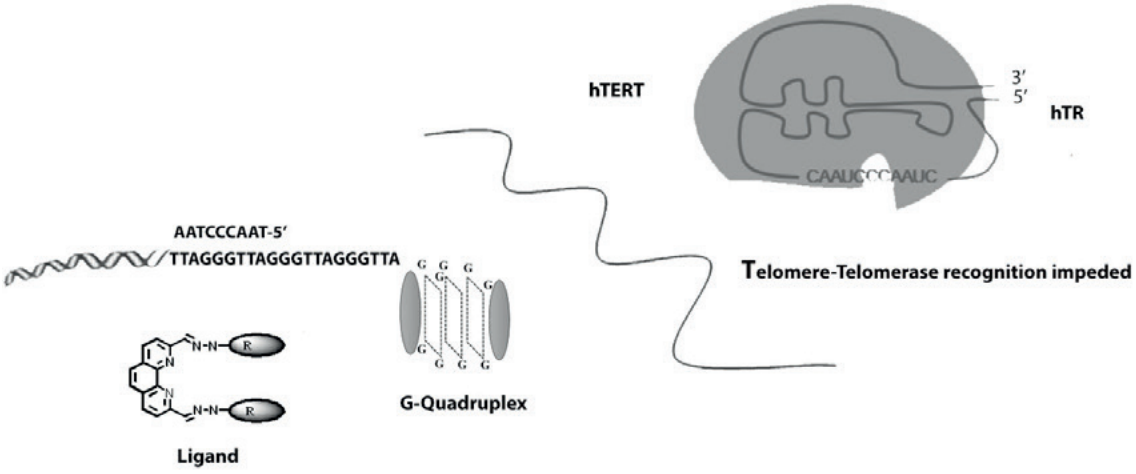
Human telomerase is a ribonucleoprotein, widely studied, responsible for maintaining the length of telomeres by adding repetitive DNA fragments with the sequence (TTAGGG)n (1). It has been found that the activity of human telomerase is very significant in approximately 85% of cancer cells, preventing them from reaching the stage of senescence or experiencing apoptosis.(2) Therefore, one of the multiple therapeutic applications associated with the design of G-quadruplex DNA ligands is related to the inhibition of telomerase. It has been shown that telomeric G-DNA stabilization by small molecules indirectly inhibits the activity of the telomerase causing the disconnection of the telomeres and, consequently, apoptosis or senescence in tumor cells.(3)

The aim of this work is designing and synthesizing novel telomeric G-DNA ligands that may be able to inhibit telomerase activity. Based on structural studies and previous results, it is possible to rationalize the general structural features of novel molecules. We have selected 1,10-phenanthroline as the heterocyclic core, which has been suitably modified to increase its ability to stabilize G-quadruplex DNA. The designed molecules contained different side chains attached to the nucleus through hydrazine bonds and incorporate other DNA binding motifs such as guanidinium or anthracene or acridine subunits. Our recent results on G-DNA stabilization and biological activity will be presented.



Acknowledgements

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INNOVATIVE SYNTHETIC METHODOLOGY: ACOUSTIC DROPLET EJECTION ENABLED AUTOMATED REACTION

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New drugs are often discovered by sequential optimization of properties involving the synthesis and testing of many different chemicals, and current organic synthesis are always performed in a sequential fashion on a material-consuming scale. This whole process can be time-consuming thus slowing down the drug discovery process and also be a waste of resources. There is an urgent need for acceleration and miniaturization of synthetic organic chemistry.

Here, for the first time, we introduce acoustic droplet ejection technology (ADE technology) into small-molecule synthesis. ADE technology can transfer reagents in complete automation by touchless nL-volume droplet. In the following work, we apply ADE technology in 16 different multicomponent reactions(MCR) and then do quality control analysis(SFC-mass). In brief, this ADE technology enables us to finish 1536 reactions in only a few days (4 plates, each plate with 384 wells, one reaction takes place in one well). Afterwards, we do SFC-mass analysis also in an automatic way by using the software programme designed by our group to eventually generate a heatmap which gives an intuitive view.

It can be seen that the whole synthetic and quality control process is performed in an automated and accelerated fashion. It is conceivable that this ADE technology will have a great potential in speeding up the drug design process and also other related fields. This potential can change and reform the traditional ways of working.

INTO THE ILK–PARVIN INTERACTION AS A NEW STRATEGY AGAINST CHRONIC KIDNEY DISEASE

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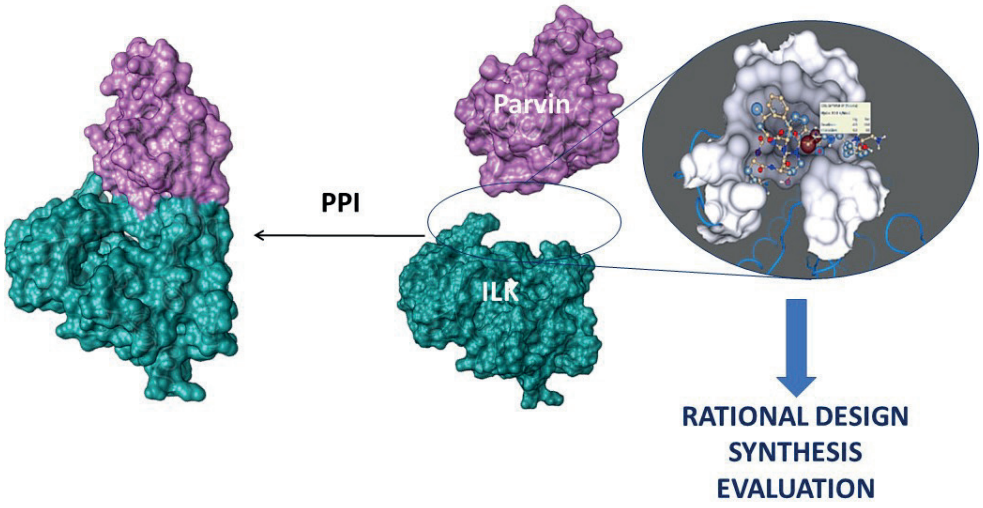
Chronic kidney disease (CKD) is the non–transmissible global cause of death that raised the most within the past 20 years. It increases the risk of all–cause mortality and may progress to end–stage of renal failure. There is no effective therapy for CKD and current approaches do not prevent its progression. Then, the search of new and validated targets against CKD has become a milestone in academic groups and industry. This pathology has been related, at least partially, to integrin–linked kinase (ILK) [1]. This is an intracellular pseudokinase which forms the ternary complex IPP (ILK–PINCH–parvin) with two adaptor proteins. On the other hand, disrupting protein–protein interactions have emerged as very promising strategy against different types of diseases due to its high selectivity and specificity. We have focused our efforts in disrupting the ILK–parvin interaction to validate this protein as target for CKD. Starting from the crystal structure and the sequences of both proteins, an extensive analysis on the interaction surface was carried out using molecular modelling approaches to identify the most favourable regions of interaction, cavities and hot–spots. These data allowed the design and synthesis of peptides for the study of this interaction using SPR and biological assays.



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UNLOCKING THE ROLE OF HK2 IN METABOLISM AND MITOCHONDRIA-INDUCED APOPTOSIS IN CANCER CELLS: A STRUCTURE-BASED VIRTUAL SCREENING VALIDATION

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Glucose is regarded as the main fuel of cancer cells and the glycolytic pathway has been demonstrated as a potential target to be explored for cancer treatment. Several enzymes involved in glycolysis, namely hexokinase 2 (HK2), are overexpressed in different types of cancer cells[1]. This enzyme is not only involved in the first and most determinant step of glycolysis and subsequently in the different branched pathways[2,3], but also in the immortalization of cancer cells. When catalytically active, HK2 is able to bind to the voltage-dependent anion channel (VDAC) in the mitochondrial outer membrane, preventing the normal pro-apoptotic signalling. HK2-VDAC disruption should promote the binding of pro-apoptotic proteins to VDAC, therefore enhancing apoptosis in cancer cells[4].

For this reason, the inhibition of the HK2 catalytic centre is proposed as a strategy to reduce the main source of energy to cancer cells, thus significantly decreasing cancer cell proliferation, avoiding HK2 binding to VDAC, and enhancing the apoptosis process. As an effort to find hit compounds able to interfere with the HK2 catalytic activity, a structure-based drug design strategy was implemented, leading to the virtual screening of several general databases such as DrugBank (~2000 molecules), NCI (~265 000 molecules), Chemoteca (~800 molecules) and some specific databases of natural product derivatives such as Ambinter (~10 000 000 molecules) and InterBioScreen Natural Products (~84 000 molecules). The virtual screening was carried out using molecular docking calculations through Gold 5.20 software. Molecules were prepared using Molecular Operating Environment (MOE2016 0802) and then docked into the HK2 catalytic site. Our results have suggested 2981 molecules with the potential to act as new HK2 inhibitors. Biochemical validation of the above-mentioned protocol is being conducted with 64 selected molecules, using the ADP-Glo™ kinase assay, a luminescence-based approach. Some of these compounds have displayed comparable or higher inhibition than a known HK2 inhibitor.

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SYNTHESIS OF COMPLEX HETEROCYCLES VIA AZA-HECK CYCLAZATION/C-H FUNTIONALISATION CASCADE REACTION

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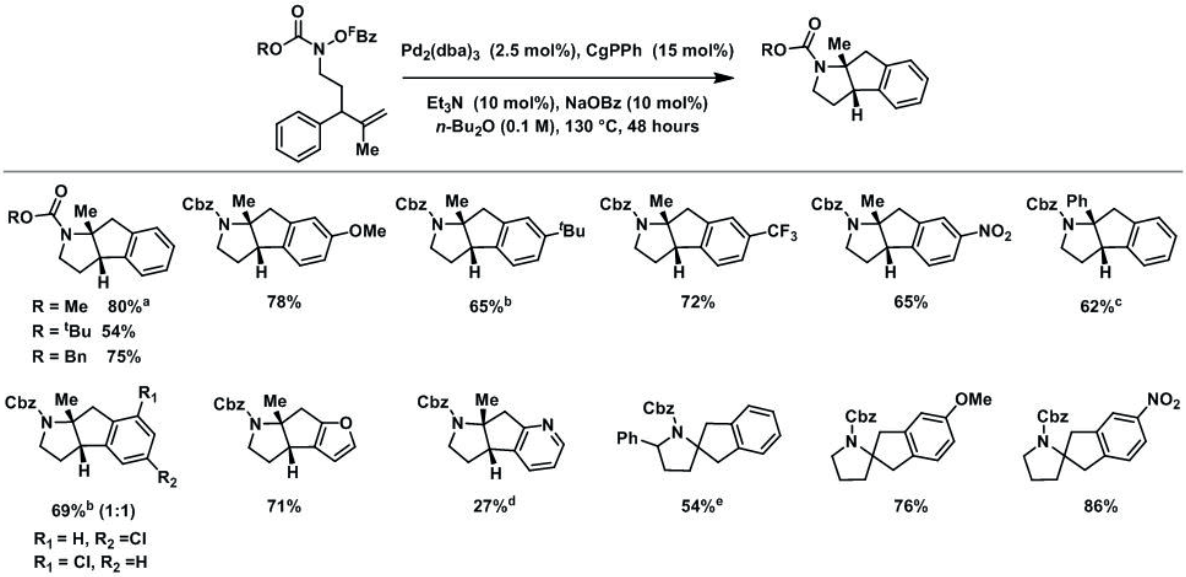
Palladium-catalysed oxidative amination processes, often termed aza-Wacker reactions, involve the nucleophilic addition of nitrogen onto an activated alkene.[1] However, transformations where the nitrogen is considered to be electrophilic are much rarer, with one prominent example being the Narasaka-Heck reaction.[2] The importance of chiral nitrogen-containing heterocycles in both natural product and synthetic drug molecules is well-known,[3] and the potential for wide application of novel aza-Heck transformations producing C(sp^3)-N bonds to access chiral *N*-heterocycles is huge. Recently, aza-Heck cascade reactions involving carbamate-based substrates were shown to be effective for accessing functionalised pyrrolidines.[4] In this regard, studies conducted in the Bower group resulted in the discovery of an interesting intramolecular aza-Heck/C–H activation cascade to afford highly substituted pyrrolidines.

After extensive optimization of the reaction conditions, the assessment of the initial substrate scope was undertaken to successfully prepare both *N*-substituted fused- and spyropyrrolidines (Table 1). Methyl and benzylcarbamates work very efficiently, while a *tert*-butyl substitution significantly decreases the yield. Benzylcarbamate was chosen due to its more feasible deprotection for further modifications at the nitrogen atom of the pyrrolidine cycle. Electron withdrawing and electron donating substituents can be handled in the aromatic ring and replacement of the phenyl ring for a heteroaromatic ring can also be done. Moreover, even though our attempts to perform the reaction enantioselectively have been unsuccessful so far, we are still aiming towards this goal. Additional examples are currently being prepared to broaden the scope, as well as experiments to validate our mechanistic hypothesis. This type of reaction cascade has the potential to produce (hopefully enantioenriched) pyrrolidines possessing tetra-substituted centres. This type of transformation is highly sought after in the pharmaceutical industry.



Reactions run on a 0.1 mmol scale; a: reaction time 24 h; b: reaction time 72 h; c: 0.047 mmol scale; d: 0.077 mmol scale, 50 mol % of CgPPh; e: 0.049 mmol scale, 50 mol % of CgPPh

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL SUBSTITUTED PURINE ISOSTERS AS EGFR KINASE INHIBITORS, WITH PROMISING PHARMACOKINETIC PROFILE AND IN VIVO EFFICACY

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Epidermal Growth Factor Receptor (EGFR) is the first member of the HER-family of receptors, consisting of four members (HER1-4, ErbB1-4), which are key regulators of important cellular functions and have been implicated in a number of the most lethal tumors [1]. Lapatinib (Fig. 1A), an approved drug, acts as dual EGFR/HER2 inhibitor and is indicated for HER2 overexpressing advanced or metastatic breast cancer [2]. Taking into account the binding mode of lapatinib [3], a number of modified purines were designed by converting the central quinazoline core of the drug to purine isoster (Fig. 1C, I-III) or purine (Fig. 1C, IV) hinge binders in order to investigate the effect of an isosteric replacement of the quinazoline core by a ring system with the capacity to accommodate additional hydrogen bonds with the kinase hinge (Fig. 1B-C).

For the synthesis of the compounds, suitably substituted pyridine or pyrimidine derivatives were used as starting materials, while each group of derivatives required its own synthetic procedure. The target compounds were evaluated for their direct inhibitory action on the intracellular receptor kinase domain, as inhibitors of receptor phosphorylation at the cellular level, and for their cytotoxicity in the non-small cell lung cancer cell line A549 and breast cancer HCC1954, which are associated with overexpression of $EGFR^{WT}$ and HER-2, respectively. The most potent derivatives were further studied for their cellular uptake levels and *in vivo* pharmacokinetic properties. One compound distinguished among the others as it displayed a noteworthy pharmacokinetic profile as well as higher intracellular accumulation in comparison to lapatinib in the A549 cells, possibly due to its higher lipophilicity. This compound was finally assessed for its efficacy in an EGFR positive xenograft model, where it successfully inhibited tumor growth, with similar efficacy with that of lapatinib and with minimal phenotypic toxicity.

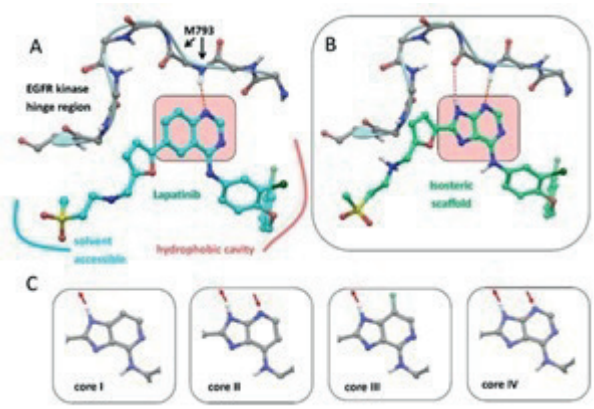

Fig. 1. A) A simplified depiction of the experimental binding mode of lapatinib in EGFR kinase domain. **B)** The designed isosteric modification of quinazoline into a purine-like system carried by the novel analogues. **C)** The four distinct heterocyclic ring systems considered and evaluated in this study.

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PPARγ AS A NEW TARGET OF THYROID HORMONES

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The signal transduction pathways of thyroid hormones were thought to be well investigated until the early 2000s when several nongenomic modes of action, that are independent of nuclear thyroid hormone receptor (TR), have been observed. Metabolites of L-thyroxin (T4) and triiodothyronine (T3), termed nonclassical thyroid hormones, were found responsible for these effects after being falsely considered as inactive products of metabolic breakdown.[1] Decarboxylated thyronamines, for example, can cause acute bradycardia and hypothermia via G-protein coupled trace amine receptors.[2] Furthermore, interaction of deaminated triiodothyroacetic acid (Triac) and tetraiodothyroacetic acid (Tetrac) with integrin αvβ3 receptor has anticancer properties.[3]

We studied, whether thyroid hormones have additional genomic modes of action by activation of other nuclear receptors. Here we report the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) as a new molecular target of the complex thyroid hormone signalling network. The ligand activated transcription factor is a major regulator of adipocyte differentiation, lipid metabolism, glucose homeostasis, and inflammation.[4,5]

We detected strong PPARγ activation by several classical and non-classical thyroid hormones with varying potencies. Extensive in vitro studies involving specific hybrid reporter gene assays, isothermal titration calorimetry, knockdown experiments, adipocyte differentiation experiments and co-crystallisation unambiguously confirm PPARγ as molecular target of several thyroid hormone metabolites.

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COMBINING METAL CHELATING AGENTS TO ACQUIRE DUAL INHIBITORS OF FLAVIVIRIDAE VIRUSES AND TRYPANOSOMA SPECIES

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Infections with *Flaviviridae* viruses, such as Hepatitis C virus (HCV) and Dengue virus (DENV) pose global health threats. Infected individuals are at risk of developing chronic liver failure or haemorrhagic fever respectively, often with a fatal outcome if left untreated. Diseases caused by tropical parasites of the *Trypanosoma* species, *T. brucei* and *T. cruzi*, constitute significant socioeconomic burden in sub-Saharan Africa and continental Latin America, yet drug development is under-funded. Anti-HCV chemotherapy is associated with severe side effects and high cost, while Dengue has no clinically approved therapy and antiparasitic drugs are outdated and difficult to administer. Moreover, drug resistance is an emerging concern. Consequently, the need for new revolutionary chemotherapies is urgent.

Previous studies by our group have resulted in compounds carrying metal chelating moieties that demonstrated a highly promising inhibition capacity against either pathogenic viruses, including influenza and HCV,[1] or parasites of the *Trypanosoma* genus.[2] By utilizing a structure-based approach, we combined two distinct chemical entities with proven antiviral and trypanocidal activity into a novel hybrid scaffold, attached by an acetohydroxamic acid group ($CH_2CONHOH$), with the aim of acquiring molecules with dual target potential, through inhibition of an essential metalloenzyme.

Here we report the design and synthesis of a series of compounds described as bicyclic-substituted hydantoin analogues. Several modifications were undertaken to further explore the structure activity relationships and confirm the pivotal role of the acetohydroxamic acid metal binding group. The novel synthesized compounds were evaluated for their potency against three HCV genotypes (1b, 3a, 4a), DENV and two *Trypanosoma* species (*T. brucei*, *T. cruzi*). They exhibited significant EC_{50} values and remarkable selectivity indices.[3] Biological results suggest that the novel class of the metal chelators, presented herein, offers a highly promising starting point for the design of potent multifunctional drugs.

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STUDIES TOWARDS THE TOTAL SYNTHESIS OF THE ANTI-INFLAMMATORY DITERPENOID NEOROGIOLTRIOL AND DERIVATIVES

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A number of natural products derived from marine organisms have been reported to exhibit a broad spectrum of pharmacological activity, including anti-inflammatory effects.[1] Algae, and in particular red algae, represent a rich source of different secondary metabolites, the majority of which consists of acetogenins, halogenated diterpenes and sesquiterpenes.[2]

Recently, we isolated neorogioltriol (Fig 1), a new tricyclic brominated diterpenoid with analgesic activity[3] from the organic extract of the red algae Laurencia glandulifera. Subsequently, we investigated the anti-inflammatory activity of neorogioltriol in vitro on lipopolysaccharide (LPS)-treated Raw264.7 macrophages and in vivo using carrageenan-induced inflammation in the rat paw. The in vivo study demonstrated that the administration of 1 mg/kg of neorogioltriol resulted in a significant reduction of carrageenan-induced ratedema.[4] Thus, we set out to identify the molecular features of neorogioltriol responsible for its anti-inflammatory properties. This objective can be achieved either by chemical modification of neorogioltriol or through total synthesis and evaluation of the biological activity of intermediates. The second approach, though more time-consuming, offers the possibility of synthesizing a variety of analogues of the natural product on a large scale without having to collect it from the marine environment. Therefore, we embarked on the total synthesis of neorogioltriol using a convergent approach. In the current work we will present our synthetic efforts towards this goal as well as the preparation of derivatives of the natural product in order to obtain structure activity relationships.

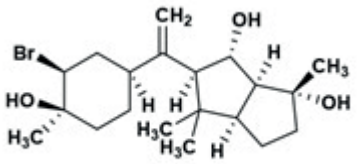

Figure 1. Structure of neorogioltriol

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PR39-BASED PEPTIDOMIMETICS AS ALLOSTERIC INHIBITORS OF PROTEASOME ACTIVITY

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The proteasome is responsible for degradation of most of the proteins in the cytoplasm and nucleus of eukaryotic cells. Due to the broad spectrum of its substrates, the proteasome controls critical biological processes, such as cell cycle progression, apoptosis, signal transduction, transcription, antigen presentation and oncogenesis [1]. Because of implication of the proteasomal system in the cellular processes, proteasome has become in recent years an attractive target for drug development. It has been discovered that malignant cells are more susceptible for the proteasome inhibition than normal cells, therefore the proteasome inhibitors have found application as anticancer agents. Most of the known compounds inhibiting the proteasome activity are competitive covalent inhibitors interacting with the catalytic centers of the enzyme, non-selectively blocking degradation of all the substrates. Three of these inhibitors are currently approved drugs for the treatment of hematologic malignancies, but they can cause many side effects [2-3]. Additionally, many patients develop resistance to these drugs, at least partly related to a mutation in the proteasome catalytic subunit β5. Allosteric inhibitors could provide more precise and specific control of the proteasome, thus displaying lower toxicity, because they do not compete with the substrate for access to the active site of the enzyme.

In search for allosteric inhibitors of the 20S proteasome we focused on the *N*-terminal fragment of PR39. It is a naturally occurring, proline-and arginine-rich peptide. In the contrast to the conventional proteasomal inhibitors, PR39 inhibits the proteasome activity in a noncompetitive manner. It is known that 11-residue-long *N*-terminal fragment of PR39 is responsible for its interaction with the enzyme [4]. We optimized structure of peptide PR11 to obtain more efficient and stable under proteolytic conditions inhibitors of the proteasome activity. The results of the biological activity studies as well as degradation tests will be presented.

Acknowledgments:

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NOVEL 6-SUBSTITUTED PICOLINONITRILE DERIVATIVES: SYNTHESIS, CHARACTERIZATION AND TUBERCULOSTATIC ACTIVITY

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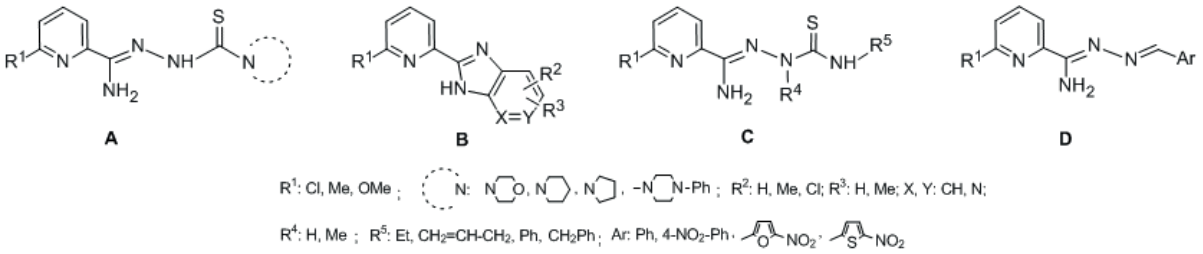
Previously we reported a tuberculostatic activity of some hydrazinecarbodithioic acid esters and amides derived from azinamidrazones or azinocarbohydrazides [1,2]. Then we described the synthesis of novel 4-phenyl and 4-phenylpiperazinpicolinonitrile derivatives [3,4]. Here we disclose the results of our research on the synthesis of new picolinonitrile derivatives substituted with various groups at the 6 position. The starting picolinonitriles were transformed into methyl picolinimidates while treated with DBU in methanol. Methyl imidates were used in the reaction with few cycloalkylamino-1-carbothiohydrazides to thiosemicarbazides (**A**). Methyl imidates also underwent the reaction with ammonium polysulfide giving corresponding thioamide which was subjected to reaction with various 1,2-diamines to benzimidazoles (**B**).



Then methyl imidates were also converted into amidrazones and methylamidrazones under the reaction with hydrazine hydrate or methylhydrazine. Both types of products underwent the reaction with various isothiocyanates giving thiosemicarbazides (**C**). Moreover, amidrazones was condensed with various aldehydes to corresponding imines (**D**). All the newly synthesized compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra. They have been also tested for tuberculostatic activity *in vitro* against *M. tuberculosis* strains: H_{37} Rv standard strain and Spec. 210 resistant strain.

This project was funded by the National Science Centre (Cracow, Poland) on the basis of decision number DEC-2017/25/B/NZ7/00124

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FROM EASILY ACESSIBLE BIOMASS TO KEY BIOACTIVE SCAFFOLDS

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Preparation of biologically active products from biomass allows for cheaper and accessible drug products. With this in mind, our group has been involved in the development of synthetic procedures to diversify biomass derivatives. In particular our group prepared 5-hydroxymethylfurfural[1] from fructose or glucose and developed a family of antitumoral triarylmethanes[2] from this monomer and recently prepared a family of highly complex δ-Lactone-fused cyclopentenones[3] (CPs). Also furfural is currently prepared in industrial scale from lignocellulosic material and our group have developed methodologies for the preparation of *trans* -4,5-diaminocyclopentenones including a very mild procedure in aqueous media[4]. This CPs show remarkable antimicrobial activity[5]. Further derivatization of the CPs through a Michael addition allow the formation of new families of antitumoral CPs[5]with optimal drug-like properties. In this way we hope to show the potential of biomass in the development of valuable scaffolds for Medicinal Chemistry that are in pair with the environmentally friendly demands.

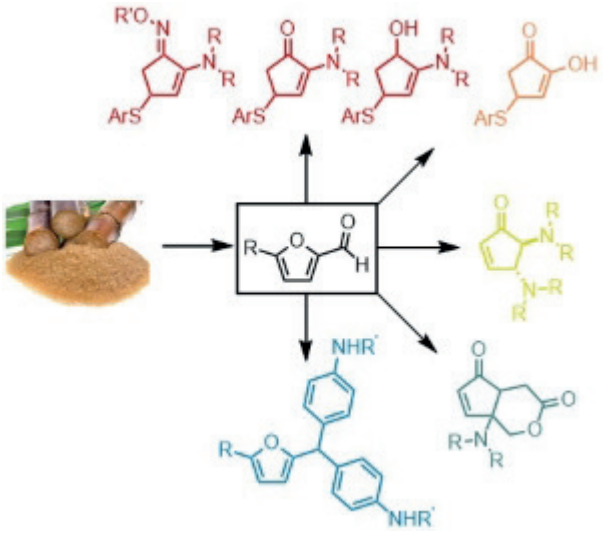

Fig 1. Transformation of biomass to bioactive scaffolds

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5) Manuscript submited

BIOISOSTERIC REPLACEMENTS IN DRUG DISCOVERY

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Introduction of more sp3 character in the design of new bioactives compounds has become a must for many scientists in life sciences. This stems out from the observation that, despites millions of flat aromatic molecules could be made and have been made using palladium-catalyzed chemistry, the chemical space covered and results of screening did not quite match the effort. More three-dimensional character, more conformational restriction etc. would allow - with the help of rational design and chemo-informatics - to reach our goal faster.

However, the addition of one more dimension to the equation meant more chemical space coverage but also A LOT more complexity in the design and synthesis of suitable building blocks, which jeopardize the whole concept. The design of efficient accompanying methodologies is therefore strongly needed. We will describe new synthetic strategies that have been designed and optimized to grant access to a large variety of small conformationally-restricted molecules, such as spirocycles and bicyclo[1.1.1]pentanes, but also other cage motifs such as cubanes and bicyclo[x.y.z]alkanes. New chemotypes including fused sp2/sp3 scaffolds will also be presented.

Examples of how we tackled and solved the scale-up challenges of these new series will be presented as our goal is to develop readily-accessible solutions with minimal downstream headaches in development.

The introduction of these new motifs in fragment libraries and how they allow the coverage of more chemical space will also be covered.

POTENT INHIBITORS OF TUMOR ASSOCIATED CARBONIC ANHYDRASES IX AND XII

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Carbonic anhydrases (CA) are ubiquitous zinc containing enzymes. In humans α-CA catalyze a reversible hydration of carbon dioxide, and thus ensure regulation of intracellular pH and control transport of CO_2. There are 15 isoforms of α-CA. However, only two of them – CA IX and CA XII are overexpressed in hypoxic cancer cells, and they are involved in the control of optimal pH for survival and growth of tumor cells. Consequently, selective inhibition of CA IX and CA XII would result in blocking of cancer cells development without undesirable side effects. Good inhibitory activities of CA IX and CA XII were demonstrated of coumarins and their bioisosteres - sulfocoumarin derivatives. [1-4] Looking for a new selective CA IX and CA XII inhibitors we designed heterocyclic analogues of sulfocoumarin **1** containing pyridine and thiophene rings. As well as benzoxepinones were designed as analogues of coumarin.

The synthesis of sulfocoumarin heterocyclic analogues **1** and benzoxepinones [5] as well as CA inhibition data will be discussed.

Acknowledgements

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SYNTHESIS OF NOVEL METALATED-OLIGONUCLEOTIDE CONJUGATES BY CLICK CHEMISTRY AS POTENTIAL ANTICANCER AGENTS: SYNTHESIS AND PRELIMINARY BIOLOGICAL STUDIES

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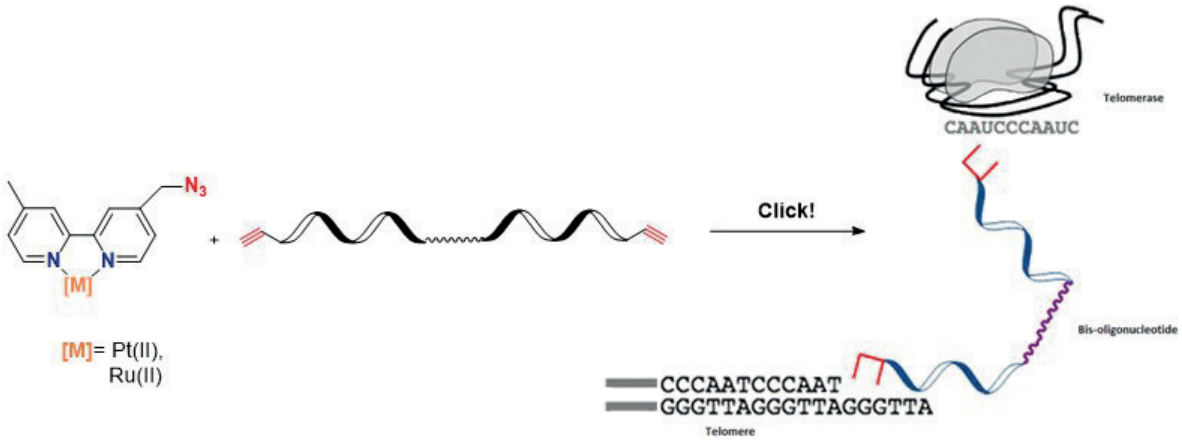
The search of anticancer agents with an increased activity and selectivity, and ideally less toxicity than cisplatin is an area of intensive investigation. Among the variety of alternative drug design strategies, the incorporation of polyaromatic DNA intercalating agents, the modification of the metal coordination sphere to include biologically active molecules [1] or the preparation of modified oligonucleotides are significant examples. As a matter of fact, in the last years, increasing efforts have been made to develop bioconjugate systems composed of nucleic acids and PNAs covalently tethered to different metals, thus paving the way for the establishment of a variety of novel applications in biomedicine [2].

One of the goals of our present work is to assemble metalated-oligonucleotide conjugate systems capable of carrying out a dual inhibition of the telomerase-telomere system, by the simultaneous recognition of the two components in an in vivo setting. Specifically, we propose the attachment of water-soluble metal complexes of Pt(II) or Ru(II) with modified oligonucleotides containing one or two alkyne groups by the use of the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction or "click chemistry" [3].



In this communication, we report our preliminary results on the synthesis, system optimization and characterization of these complex multifunctional conjugates, including recent data on cell permeability and biological activity.

Acknowledgements: Funding from Ministerio de Ciencia, Innovación y Universidades (Grant CTQ2015-72625-EXP-AEI) and from Comunidad de Madrid-European Social Fund (Youth Employment Initiative, YEI, PEJ-2017-AI/SAL-6160) is gratefully acknowledged.

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TARGET DECONVOLUTION OF TORIN2 IN PLASMODIUM FALCIPARUM USING AFFINITY-BASED PROTEIN PROFILING

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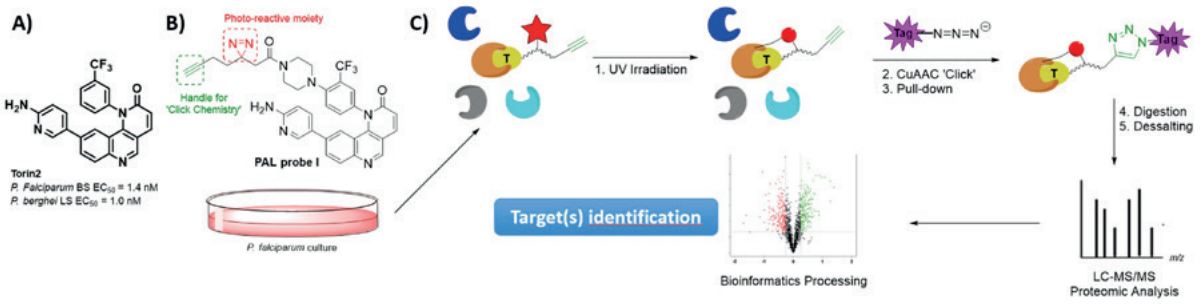
Despite the best efforts and investment from the last decade, Malaria's death toll still amounts to nearly half a million a year with no reduction of the diagnosed cases in the last 2 years and parasite resistance reported to every class of drugs in clinical use. This makes this protozoan infection a major public health concern mainly in the tropical regions of the globe [1].

To overcome these hurdles, it is critical to do advance new drugs with different mechanism of action (MoA). With this in mind, we have already disclosed Torin2, known as an ATP-competitive mTOR kinase inhibitor [2], as a potent antimalarial lead compound that possesses *in vivo* activity against both blood and liver stages. This activity was shown to be independent of the host mTOR pathway and unrelated to the MoA of current antimalarials in the clinic [3].

Here, we report the development of Torin2 photoaffinity-based probes, to deconvolute the molecular target(s) of this compound in the parasite. This was achieved through the modification of the core scaffold with a photocrosslinker and a handle suitable for 'click chemistry'. Furthermore, we disclose the application of these chemical tools in a mass spectrometry-based proteome profiling of *P. falciparum* lysates and live cultures of the disease's blood stage (Scheme 1). The results obtained are fundamental for the optimization of Torin2-based compounds as a new alternative to current antimalarials, a key breakthrough to address the existing therapeutic gap.



Scheme 1: A) Torin2 hit compound; B) Structure of the Photoaffinity labelling probe I, derived from Torin2 by the introduction of a diazirine photoreactive moiety (in red) and a terminal alkyne handle for CuAAC chemistry (in green); and C) schematic overview of the methodology applied for *P. falciparum* cell-based proteome profiling. In red: diazirine before (star) and after (circle) irradiation. In pink: TAMRA and/or Biotin azide capture reagents.

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SYNTHESIS OF NOVEL 2-SUBSTITUTED INDOLE DERIVATIVES AS POTENTIAL ANTITUMOUR AND ANTIBACTERIAL AGENTS

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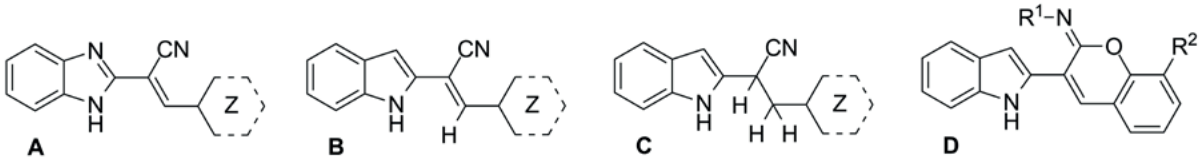
The indole moiety represents an extraordinary fragment in several promising classes of compounds with an interesting pharmacological profile. 2-substituted indoles have been shown to possess spasmolytic, hypotensive, antioxidative, tuberculostatic, insecticidal and anticancer activities.

Recently, we have described syntheses and pronounced antitumour properties of 3-arylacrylonitriles either with triazole or benzimidazole substituents in position 2 of the acrylonitrile moiety [1][2]. In particular, 2-benzimidazole substituted acrylonitriles of type **A** were effective at inhibiting the growth of various human cancer cell lines *in vitro*. Additionally, these compounds have been found to be active against *Staphylococcus epidermidis* and *Staphylococcus aureus*. With the above information in mind, we have decided to prepare a new series of 2-substituted indole analogues (structure **B**) to identify compounds with potential antitumour and/or antibacterial activities. To investigate the importance of the acrylonitrile double bond on the biological activity, derivatives lacking this group have also been synthesized (structure **C**). It should be noted that antitumour activity also exhibit variously substituted imino-coumarins [3]. Therefore we reasoned that compounds synthesized by linking indol-2-yl moiety compounds with 2-imino-coumarin ring system could be effective as potential antitumour agents (structure **D**).



R^1 = H, benzoyl, phenylsulfonyl, phenylcarbamoyl; **R**^{2} = H, Me, OMe, Cl; **Z** = aryl, heteroaryl

The structures of novel 2-substituted indole derivatives were confirmed by IR, NMR and MS spectroscopic data as well as single X-ray analysis.

The *in vitro* antitumour properties of the obtained compounds were tested at the Department of Medicinal Chemistry, University of Greifswald (Germany) and National Cancer Institute (USA). The prominent compound with remarkable anticancer activity (GI_{50} = 0.26-6.60 μM, TGI = 0.64-9.49 μM) to all investigated human tumour cell lines was (*Z*)-3-[4-(dimethylamino)phenyl]-2-(1*H*-indol-2-yl)acrylonitrile of type **B** (**Z** = 4-$(CH_3)_2$N-C_6H_4). The newly prepared compounds were also evaluated for their potential antimicrobial activities against Gram-negative and Gram-positive bacteria. The greatest antibacterial activity displayed 2-(1*H*-indol-2-yl)-3-(1*H*-pyrrol-2-yl)acrylonitrile of type **B** (Z = pyrrol-2-yl).

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DESIGN, SYNTHESIS AND ACTIVITY OF BIOMIMETIC MACROCYCLIC INHIBITORS OF HUMAN CATHEPSIN D

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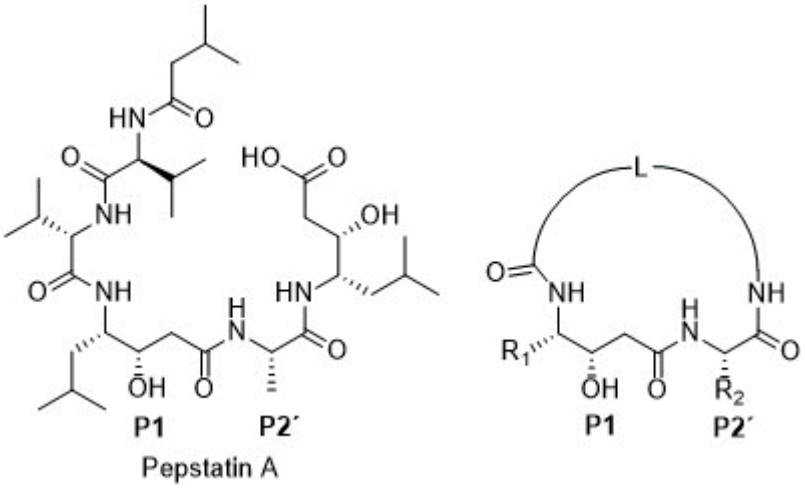
Human cathepsin D (CatD) is a pepsin-family aspartic protease, which is involved in many physiological and pathological processes in human. It is overexpressed in breast cancer cells and associated with tumor progression and metastasis. CatD inhibitors were proposed as potential cancer therapeutics and many compounds have been synthesized.

In this study, we report the development of macrocyclic inhibitors inspired by natural inhibitor of CatD, Pepstatin A. The cyclic scaffold was designed to mimic spatial conformation of the minimal pseudo-dipeptide binding motif, while removing unnecessary amino acids and replacing them with a suitable bridge connecting P2 and P3´ positions.



Reported compounds are composed of three sub-units linked together. The first sub-unit (2-hydroxy-3-amino acid) contains the transition state isostere (hydroxy group), which interacts with the active site aspartates. The second sub-unit contains R_2 substituent filling the S_2´ sub-site, while the third one is a linker (L) connecting the first two units and interacting with the large hydrophobic S2-S3´ site of the enzyme binding cleft. Library of over 30 compounds was employed for scaffold optimization. Synthesis and inhibitory potency of these compounds with variable size of the bridge and various side chains in P1 and P2´ positions will be reported.

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF TETRAHYDROISOQUINOLINE/TETRALONE DERIVATIVES AGAINST TRYPANOSOMA BRUCEI RHODESIENSE

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Human African Trypanosomiasis (HAT) is a neglected parasitic disease inherent to the African continent. It is estimated that there are around 10 000 reported cases and that 65 million people are at risk of contracting the disease.[1] Of particular interest is the rhodesiense HAT (rHAT) caused by T. b. rhodesiense. Though only accounting for 2% of reported cases in humans, rHAT is characterised by its unique zoonosis as well as rapid progression towards fatality within six months if left untreated.[2] Currently, there are no indications for treating animals infected with T. b. rhodesiense. As for humans, the only therapeutic option for rHAT is melarsoprol – an organoarsenic drug with treatment-associated mortality[3] – necessitating for the development of a more effective but safer alternative against T. b. rhodesiense.

In the past, our group established a comprehensive SAR of tetrahydroisoquinoline-derived analogues that show low micromolar activity towards the organism of T. b. rhodesiense itself.[4] This work presents a SAR study of novel tetralone-derivatives as well as improved rendition of tetrahydroisoquinoline analogues that target T. b. rhodesiense (Figure 1).

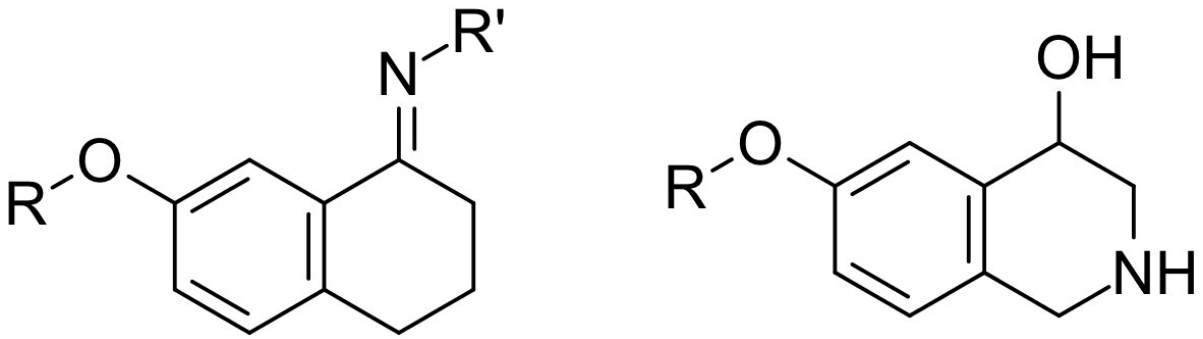

Figure 1. Analogues studied for antitrypanosomal activity.

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DISCOVERY OF SMALL-MOLECULE MODULATORS OF 14-3-3 PPIs VIA DYNAMIC COMBINATORIAL CHEMISTRY

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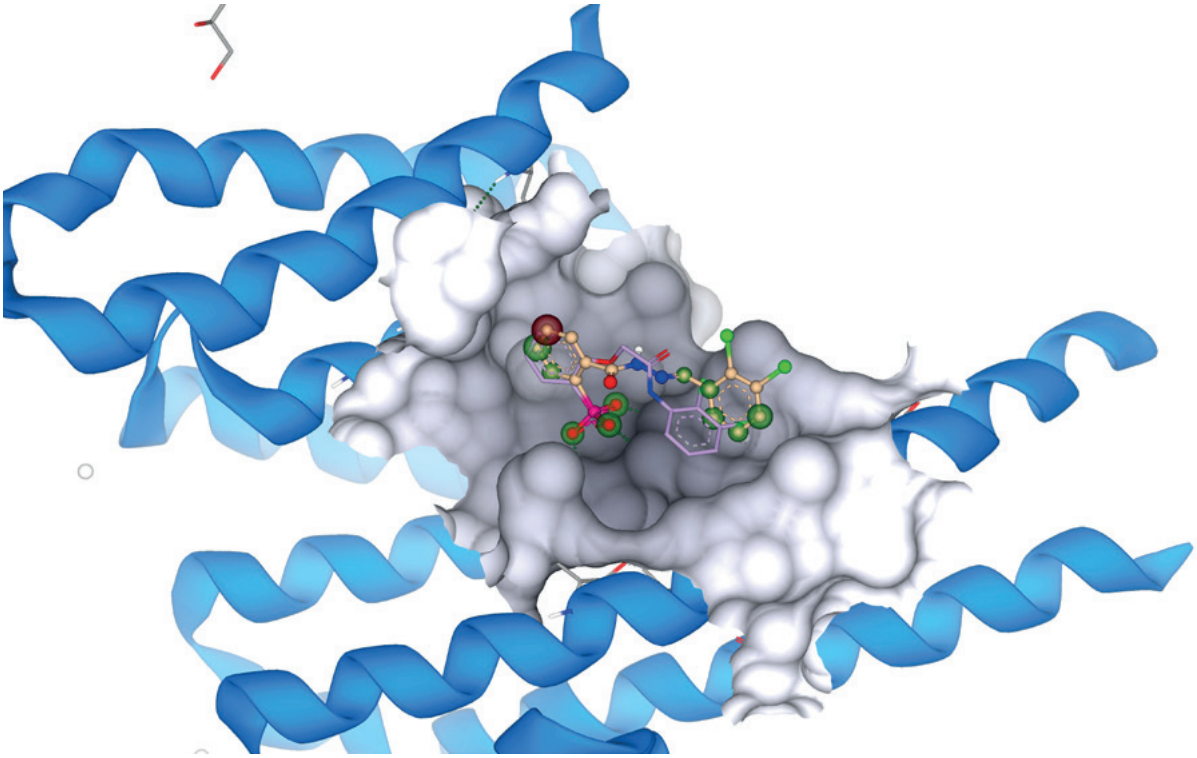
3) Laboratory of Chemical Biology and Institute of Complex Molecular Systems (ICMS), Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands

Protein-Protein Interactions (PPIs) can be found in many biological processes. It is assumed that between 130,000 and 600,000 PPIs exist, some play a role in carcinomas others for example in cell-cycle regulation. The 14-3-3 protein family is known for its PPIs, as it is implicated in several diseases and biological processes. Proteins of this family do not have any enzymatic activity, however, they interact and regulate the activity of other proteins.[1] Finding modulators, which could stabilize or inhibit [2] the PPIs, would constitute a tool to modulate these interactions and possibly interfere with undesired biological processes by targeting the corresponding PPIs. Dynamic Combinatorial Chemistry (DCC) is a powerful tool to identify biologically active compounds. The strength of this technique is the amplification of the best binders by the target. We pioneered, DCC for the identification of small-molecule stabilizers of 14-3-3 proteins, representing its first application to a PPI. To mimic a typical PPI of 14-3-3, we used synaptopodin, a 21 amino acid long peptide, in complex with 14-3-3. The activities of the amplified hits of the DCC experiment were confirmed via surface plasmon resonance (SPR) studies.[3] Optimization of promising compounds and crystallography studies are ongoing.



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DEHYDROABIETYLAMINE-BASED CELLULOSE NANOFIBRIL FILMS: A NEW CLASS OF SUSTAINABLE BIOMATERIALS FOR HIGHLY EFFICIENT, BROAD-SPECTRUM ANTIMICROBIAL EFFECTS

Ghada Hassan (1), Nina Forsman (2), Xing Wan (3), Leena Keurulainen (1), Luis M. Bimbo (6), Leena-Sisko Johansson (2), Nina Sipari (4), Jari Yli-Kauhaluoma (1), Ralf Zimmermann (5), Susanne Stehl (5), Carsten Werner (5), Per E. J. Saris (3), Monika Österberg (2), Vânia M. Moreria (1,6)

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Antibacterial coatings are needed in the manufacturing of biomedical devices and tissue engineering-related materials which continuously suffer from microbial colonization.[1] They are also needed to limit the destructive effect of biofilms accumulating onto various surfaces, causing health risks and losses in several industries including food, water and paper. [2]

Nanofibrillated cellulose (CNF) is a renewable biomaterial with high potential to reach commercialization. [3] Currently, it is investigated for its potential applications in the biomedical field due to its biocompatibility, low cytotoxicity and unique chemical properties. [4]

Abietanes, naturally occurring diterpenoids extracted from pine resin, have demonstrated antimicrobial and anti-biofilm activity. [5-6] The approach of surface protection with an antimicrobial coating material includes attaching antimicrobial compounds to a surface. [7] When linked to a surface, the antimicrobial agent is not released or consumed, providing effective and long-lasting surface protection. [8]

Herein we report the discovery of a new class of ecofriendly antimicrobial materials based on the modification of nanofibrillated cellulose (CNF) films with (+)-dehydroabietylamine (Figure 1), a commercially available diterpenic amine with weak antimicrobial activity. [9]

With a minimal surface coverage (14 - 25%) and good biocompatibility the materials exhibited outstanding antimicrobial activity against the gram positive *Staphylococcus aureus*, the gram negative *Escherichia coli*, and the methicillin-resistant *S. aureus* MRSA14TK301. The immobilization of antimicrobial diterpenes on the surface retained the original physicochemical properties of the CNF including moisture buffering and strength.

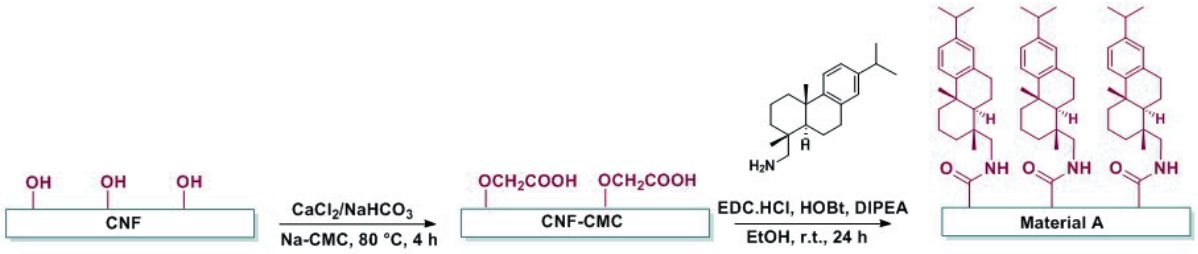

Figure 1. Example showing synthesis of CNF and (+)-dehydroabietylamine hybrid material.

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BREITFUSSINS - SYNTHESIS AND BIOLOGICAL ACTIVITY

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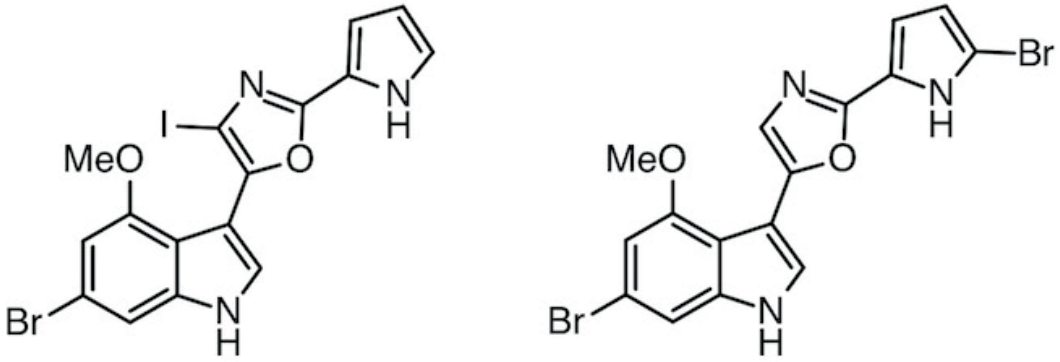
The breitfussins are halogenated highly modified dipeptide natural products that have been isolated from the Arctic, marine hydrozoan *Thuiaria breitfussi*.[1]These natural products comprise a uniqueindole-oxazole-pyrrole framework that has not been found in any other natural products. The ratio of heavy atoms to protons (approx. 2:1) made structure elucidation by spectroscopic methods challenging,[1]and the structures of breitfussin A and B were unambiguously confirmed by total synthesis.[2]Continued investigations of *Thuiaria breitfussi*has led to the identification of six new members of the breitfussin family of natural products.[3]

Extensive investigation into the biological activity of the breitfussins, has revealed that several members of this class of natural products display cytotoxic activity against some cancer cell lines. This activity has been attributed to kinase inhibition, thus the indole-oxazole-pyrrole framework of the breitfussins represents an unmatched kinase inhibitor scaffold.[3]



Breitfussin A **Breitfussin B**

Herein we report on our synthetic efforts toward the breitfussin family of natural products and detailed investigations into their biological activity in order to explore into the potential of the core structure of the breitfussins as a new scaffold for selective kinase inhibition.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL EPIGENETIC INHIBITORS TARGETING TCDAC2 FROM TRYPANOSOMA CRUZI

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5) Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz Belo Horizonte, Minas Gerais-Brazil

The American trypanosomiasis, also known as Chagas disease, has been recognized by the WHO as one of the neglected tropical diseases and is estimated to affect 8 million people worldwide.[1] This disease is caused by the protozoan parasite *Trypanosoma cruzi,* which is transmitted by triatomine bugs. Endemic in Latin America Chagas disease has spread from its original boundaries through migration and has thus become a global issue.[2] Current treatment is limited to benznidazole and nifurtimox, which are associated with severe side effects, low cure rates in the chronic stage and the emergence of drug resistance.

Histone deacetylases (HDACs) are validated epigenetic drug targets in cancer therapy and there is evidence that they can also be adressed to treat parasitic infections. Since parasitic HDACs play key roles in the modulation of parasite gene expression and therefore take an important part in parasitic infectivity and survival, they represent potential antiparasitic targets.[3]

In *T. cruzi* four zinc dependent HDACs have been identified. We focus on the *Trypanosoma cruzi* deacetylase 2 (TcDAC2), the homologous isoform of SmHDAC8 in *Schistosoma mansoni*, which has been identified as a promising target for antiparasitic drug discovery.[4-6]

A series of novel cinnamic hydroxamic acid derivatives was synthesized and tested for their inhibitory activity against parasite and human HDACs. *In vitro* experiments revealed that several inhibitors exhibited selective antiparasitic activity in *T. cruzi* and are not toxic to human cells.

Acknowledgments: This work is funded by the European Union's Seventh Framework Program for research, technological development and demonstration under grant agreement no. 602080 and by the European Regional Development Fund of the European Commission (K.H., W.S. and M.J.).

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HITTING TWO BIRDS WITH ONE STONE: PDZ-7 – A TOPOISOMERASE IIα POISON AFFECTING ACTIN CYTOSKELETON

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Anthracyclines are still a drug of choice for treatment of many tumors. Three aromatic rings forming a flat core structure make them potent DNA intercalating agents acting as topoisomerase II poisons. The presence of quinone moiety is believed to generate reactive oxygen species (ROS) which raises an issue of cardiotoxicity [1]. Furthermore, they are known substrates of ABC transporters [2]. To solve these problems while retaining the potent activity against multiple tumors we have synthesized over twenty derivatives based on the anthrapyridazone core.

The tested compounds exhibited activity in the low nanomolar range. To determine the molecular targets, we used well-established models of non-small lung cancer and acute myeloid leukemia, as well as cell-free experiments. We have found a strong correlation between DNA binding affinity and anticancer activity, which suggests DNA as the major molecular target. Three of the derivatives were exceedingly well tolerated in mice with one (PDZ-7) also showing a significant advantage in antitumor activity over doxorubicin *in vivo*.

PDZ-7 and other anthrapyridazones consistently inhibited the activity of both type I and II DNA topoisomerases *in vitro*. Induction of H2AX phosphorylation on Ser139 combined with an activation of Mre11-Rad50-Nbs1 (MRN) indicates double-stranded DNA breaks as a major effect of PDZ-7. The isolation of the stable covalent topoisomerase IIα-DNA complexes forming in presence PDZ-7 suggests this compound is a topoisomerase IIα poison. Consistently, PDZ-7 blocked DNA synthesis and induced cell cycle arrest in late S and G2 phases. Moreover, we have shown PDZ-7 interfered with actin polymerization effective in critical cytoskeleton disturbances.

Taken together, our results suggest PDZ-7 is a unique dual inhibitor of topoisomerase IIα and actin polymerization. In strike contrast to established anthracyclines, it retains cytotoxic activity against resistant cancers overexpressing ABC transporters such as ABCB1, ABCC1 and ABCG2.

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STRUCTURE-BASED DEVELOPMENT OF SELECTIVE OREXIN 1 RECEPTOR ANTAGONISTS DERIVED FROM SUVOREXANT

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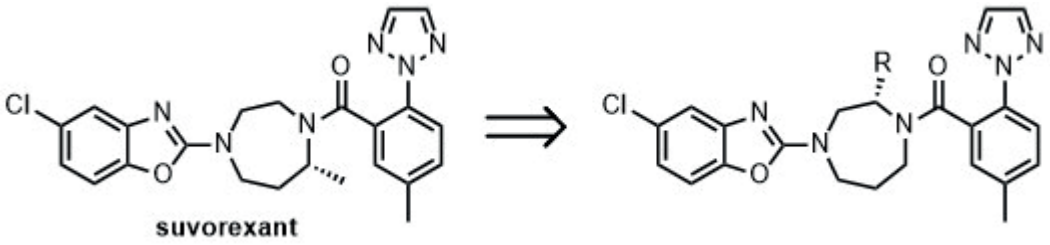
Orexins are neuropeptides that activate the rhodopsin-like G protein-coupled receptors OX1R and OX2R. The orexin system plays an important role in the regulation of the sleep-wake cycle and the regulation of feeding and emotions. The high resolution crystal structures of both receptor subtypes bound to the dual orexin receptor antagonist suvorexant provide valuable insights into the structural environment of the orthosteric binding sites.[1-2] Suvorexant is the only drug on the market targeting the orexin system and is prescribed for the treatment of insomnia.[3] There are only two non-conserved residues in the orthosteric binding site within 4 Å of the ligand. An alanine and a serine residue of the OX1R are substituted by threonine in the OX2R resulting in a slightly larger binding pocket of the OX1R compared to the OX2R's binding site. We wanted to exploit the available space in the OX1R's binding site to develop selective orexin 1 receptor antagonists based on the structure of suvorexant.

Hence, we established an enantiospecific synthetic route starting from natural or artificial amino acids for suvorexant derivatives bearing an alkyl substituent at the central homopiperazine moiety. The substituents were expected to point towards one of the non-conserved residues resulting in a steric clash with the larger threonine side chain of the OX2R. We synthesized various derivatives and determined their binding affinities to both orexin receptor subtypes in a radioligand binding assay. We were able to obtain a crystal structure of the OX1R bound to the most promising candidate of the synthesized ligands.



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COMPUTER-AIDED SELECTIVE OPTIMIZATION OF SIDE ACTIVITIES OF TALINOLOL

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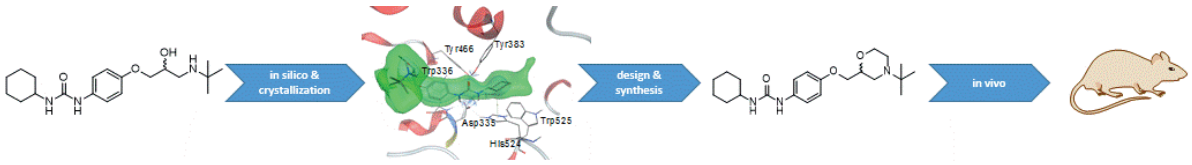
SOSA (selective optimization of side activities) is an effective way to identify promising new lead structures which will then be further optimized for the new target.[1] Following this strategy a side activity of a drug is enhanced by structural changes of the lead, while simultaneously the affinity to the original target is reduced. Clinical studies revealed that talinolol, an unselective antagonist of β adrenergic receptors, showed beneficial effects on triglycerides and cholesterol levels compared to propranolol and atenolol, which were independent of the antagonisms of the β adrenergic receptors.[2] Based on these results we performed *in silico* target prediction using web-based target deorphanization tools (HitPickV2,SuperPredand SwissTargetPrediction)[3], predicting the soluble epoxide hydrolase (sEH) as a possible target.

First, co-crystallization experiments were performed to determine the binding mode of talinolol in complex with sEH, showing no critical interactions between the hydroxyl moiety of the compound and the sEH-Hydrolase. By bridging the hydroxyl moiety with the secondary amine through a carbon linker morpholino-talinolol was generated. This new compound exhibit improved potency regarding the sEH and a dramatically reduced affinity towards the β adrenergic receptors. Since inhibition of the sEH leads to increased levels of the short living epoxyeicosatrienoic acids (EETs), which in consequence improves hyperalgesia in the context of neuropathic pain models, the efficacy of morpholino-talinolol was investigated in rat model of neuropathic pain.[4] Morpholino-talinolol blocked allodynia and this anti-nociception was sustained up to 2 h. Within this work, SOSA approach was facilitated by *in silico* target prediction in combination with X-ray crystallography, and led to identification of the new *in vivo* active sEH inhibitor morpholino-talinolol.



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THE DISCOVERY OF UNIQUE MOLECULAR PROBES FOR THE STUDY OF AMINERGIC GPCR'S FUNCTION

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The discovery of the weakly basic ligands of histamine and serotonin receptors may have been the long awaited breakthrough in the design of subtype specific ligands of aminergic receptors. These new chemotypes bind to their targets via a mechanism different than the classically established anchoring of highly basic scaffolds to Asp 3.32 residue. Despite the fact that the findings may revolutionize both the discovery of aminergic receptor targeted pharmaceuticals (approx. 25% of drugs, all highly basic) and be a valuable source of tool compounds, still little is known regarding the mechanism of non-basic ligand-receptor complex formation.
We have found weakly basic hit compounds targeting the 5-HT_{1A}, 5-HT_6,[1] 5-HT_7 and D_2 receptors. Notably, the 3-(1-alkyl-1*H*-imidazol-5-yl)-1*H*-indoles are the first known low-basicity agonists of an aminergic receptor – 5-HT_7R that are highly valuable molecular probes and potential painkillers.[2-4] Our studies on the ligand-receptor complex formation mechanism and the possible benefits regarding the ADMET properties of those molecules indicate, that a chemical space of highly drug-like molecules has been revealed.
The open question is whether it is possible to obtain non-basic ligands of all aminergic GPCR's or is it only the property of certain subtypes such as H_3, 5-HT_{1B}, 5-HT_{2A}, 5-HT_6 and 5-HT_7 receptors.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL BRD4/HDAC DUAL INHIBITORS AS EPIGENETIC PROBES

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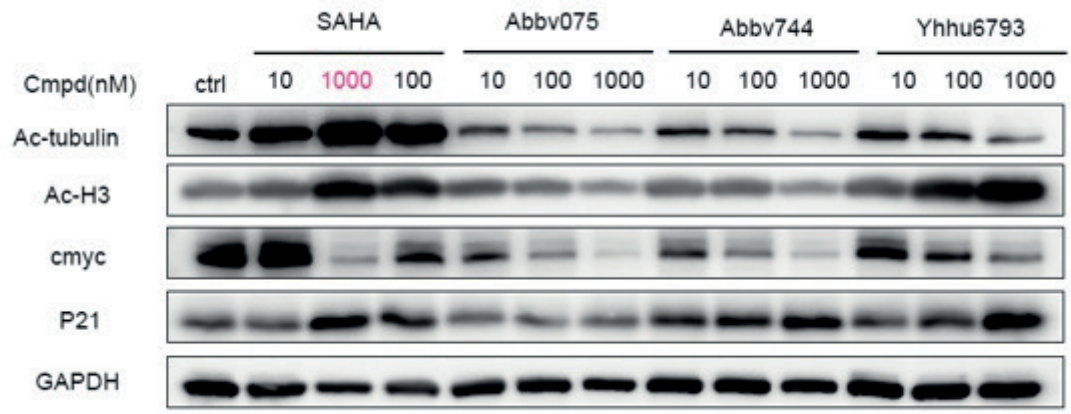
Acetylation of a histone lysine residue has been defined as a hallmark of transcriptionally active genes. Lysine acetylation catalyzed by the histone acetyltransferases (HATs) can neutralize its positive charge leading to reduced affinity of histones for negatively charged DNA or disruption of nucleosome packing and ultimately to an open, accessible chromatin structure that is able to recruit transcriptional machinery. On the other hand, acetylated lysine provides binding sites for protein recognition modules, such as the bromodomain and extraterminal motif (BET) proteins. Currently, several classes of anticancer drugs targeting the key proteins in this process have been approved and developed for clinical use, including inhibitors of histone deacetylases (HDACs) and bromodomain and extraterminal motif (BET) proteins. HDACs has been widely recognized as promising targets for therapeutic interventions and intended to reverse aberrant epigenetic states associated with cancer. However, single agent HDAC inhibitors in solid tumors remains uncertain, including breast cancer, renal cancer, prostate cancer, and head and neck cancer. Recent study showed that HDAC inhibitors promote BRD4-mediated activation of LIFR, which in turn activates JAK1-STAT3 signaling and restrains the efficacy of HDAC inhibitors in breast cancer, and BRD4 inhibition can augments efficacy of HDAC inhibitors in breast cancer, in particular the triple-negative subset. Preclinical data suggest that the combination of BET and HDAC inhibitors has strong synergy at reduced doses, suggesting a potential means of avoiding the overlapping toxicities of the two drug classes. Based on these, we designed and synthesized a series of 6-azaindole derivatives based that combineed the inhibitory activities of BRD4 and HDAC into one molecule, and in vitro anti-proliferation activities were also evaluated. Among them, yhhu6793 showed excellent anti-proliferation activity in different cell lines. In vivo study in MV-411 xenograft mice found that yhhu6793 could effectively inhibit the tumor growth. It was confirmed that yhhu6793 could up-regulate the expression of Ac-H3 and reduce the expression of c-Myc by western blot analysis. These results indicated that yhhu6793 is a potent BRD4/HDAC dual inhibitors for futher investugationn as an epigenetic probe.



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PURINE NUCLEOSIDE ANALOGS AS HIGHLY POTENT LEADS FOR THE TREATMENT OF HUMAN AFRICAN TRYPANOSOMIASIS

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Human African Trypanosomiasis (HAT) is a deadly infectious disease caused by *Trypanosoma brucei* spp. parasites. This vector-borne disease, prevalent in sub-Saharan Africa is spread via bites of infected tsetse flies. The disease course is characterized by a two-stage disease progression, linked to parasite distribution in the body. A first, often non-symptomatic stage occurs when parasites enter the haemolymphatic system. Later, when parasites cross the blood-brain barrier (stage-II), patients develop neurological symptoms such as altered sleep-wake cycles, hence the more common name for HAT being sleeping sickness.

Available therapeutics suffer from major drawbacks such as: they only show efficacy in stage-I disease; high inherent toxicity (arsenicals); the need for systemic administration, which is challenging in rural areas in Africa. Finally, drug resistance against available treatments is on the rise. This showcases the pressing need for novel therapeutic options.

Nucleoside analogues have found wide-spread use as antivirals and in oncology. While some nucleoside analogues were reported to have activity against *T. brucei* spp., systematic screening of nucleoside libraries is not a common practice. *T. brucei* parasites are unable to assimilate the purine ring (no *de novo* purine synthesis), and therefore must rely on salvage of host purines to meet their high demand. Hence, purine nucleosides analogues might interact with this highly developed salvage pathway, either as inhibitors of specific enzymes or as subversive substrates. This presents a interesting rationale to investigate purine nucleoside analogues as a means to discover new bio-active hits.

In this presentation, we will discuss the discovery of a new class of purine nucleoside analogues characterized by potent *in vitro* activity against *T. brucei*. Additionally, results from the evaluation of the frontrunner analogue in acute as well as CNS-stage mouse models of HAT will be presented. This derivative was shown to be orally bioavailable and able to cross the blood-brain-barrier, marking it as a highly promising lead for the treatment of HAT.

DISCOVERY OF 7-ARYL-7-DEAZAPURINE 3'-DEOXYRIBOFURANOSYL NUCLEOSIDE ANALOGUES AS ANTI-TRYPANOSOMA CRUZI AGENTS

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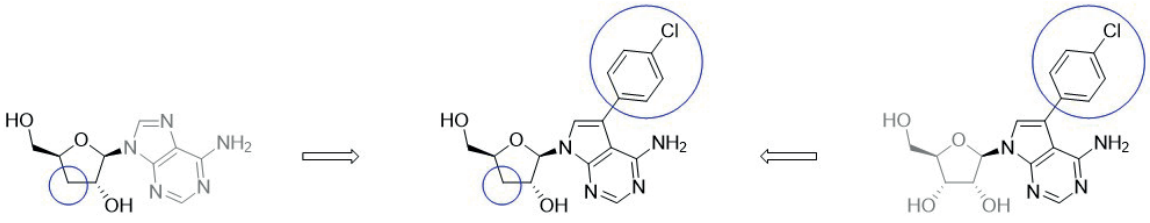
The intracellular protozoan parasite, *Trypanosoma cruzi* (*T. cruzi*) is the etiological agent of Chagas disease, a disease endemic in Latin-America, where it represents the leading cause of cardiac-related mortality. Parasites are primarily transmitted via the faeces of the Triatomine (or "Kissing bug") vector, albeit that other routes for contracting the disease such as oral, congenital and iatrogenic (i.e. via blood transfusion or organ transplants) have been documented. Originally restricted to Latin-American countries, *T. cruzi* cases have increased both in North-America, Japan, Europe and Australia as a result of increased migration, making this neglected tropical disease a significant global health concern.

Currently available treatment options (benznidazole and nifurtimox) suffer from limitations such as limited efficacy, resistance and significant side-effects, often resulting in suboptimal drug use or premature treatment discontinuation. Therefore, there is a significant need to investigate novel chemotherapeutic options, particularly in the form of new chemical entities.

T. cruzi parasites are purine auxotrophs, signifying that they rely solely on the uptake and processing of host purines, since they lack the enzymes of the *de novo* pathway. Purine nucleoside analogues could thus constitute an interesting source to find new starting points for further elaboration in medicinal chemistry campaigns.

In this presentation, we will discuss our efforts starting from cordycepin and a previously reported tubercidin analogue,[1] ultimately leading to hybrid compounds with potent *in vitro* activity against *T. cruzi*. The lead compound displayed significant activity when assayed in a mouse model of acute Chagas disease.[2]



Cordycepin
T. cruzi EC_{50}: 2.51 ± 0.22 µM

T. cruzi EC_{50}: 0.047 ± 0.006 µM

T. cruzi EC_{50}: 0.47 ± 0.25 µM

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OPEN SOURCE TUBERCULOSIS (OSTB) SERIES 3: SMALL MOLECULE INHIBITORS OF NON-REPLICATING MYCOBACTERIUM TB

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Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (*Mtb*) and is one of the top 10 causes of death worldwide.[1] The World Health Organisation estimates that 25% of the world's population have latent TB, with a 5–15% lifetime risk of those individuals falling ill with the disease due to regrowth of the dormant, non-replicating (NR) *Mtb* residing in their tissues. Therefore, treatment of the latent TB infection represents an important strategy for preventing the progression of the disease. Current treatments involve administering isoniazid, rifapentine, or rifampin over 3 to 9 months, depending on the regimen.[2] Hence, an urgent need for short-term therapies to eliminate dormant bacilli and reduce the global burden caused by TB.

Guided by open source principles, the Open Source Tuberculosis (OSTB) consortium is trying a different approach to curing TB. All data is open, and anyone can contribute.[3] Research follows the 'Six Laws'[4] with the aim of speeding up the drug discovery process. OSTB Series 3 arose from collaborative work performed by GSK and Cornell University in 2015.[5] Nine novel bactericidal scaffolds were discovered by a high-throughput screen of 270,000 compounds from GSK's library. Amongst these, **OSTBS83** was identified as a selective and potent inhibitor of NR *Mtb* with low toxicity towards human hepatocellular carcinoma cell line, HepG2 (**Figure 1a**). These desirable properties make **OSTBS83** an attractive starting point for lead optimisation. Herein, we present our structure activity relationship studies to date, with current synthetic efforts focusing on making subtle changes to the aromatic core and amide tether to improve potency (**Figure 1b**).

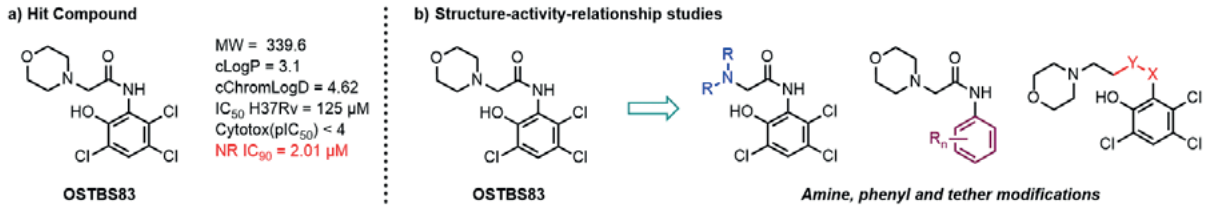

Figure 1: Lead optimisation of **OSTBS83**.

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BENZAZEPINONE DERIVATIVES AS ANTITRYPANOSOMAL DRUG CANDIDATES

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The order Kinetoplastida includes human pathogens from the genera *Trypanosoma* and *Leishmania* which cause neglected tropical diseases (NTDs) as described by the World Health Organisation (WHO)[1]. Outcomes may be fatal, e.g. Chagas' disease in chronic stage can lead to arrhythmia and sudden death[1]. As treatment is scarce, new strategies to combat these diseases are required including a chemotherapeutic approach, preferably with a target that is exclusive as well as essential to the parasitic species. These requirements are met by the enzyme trypanothione synthetase (TryS) playing an important role in the parasites' unique trypanothione-based thiol redox metabolism[2]. Previous work has shown that N^5-substituted paullones display antitrypanosomal activity as well as TryS inhibition[3]. This work aims to generate compounds with improved biological and physicochemical properties by systematic reduction and modification of the paullone structure to a benzazepinone. Initial biological testing was performed in cell-based assays using *Trypanosoma brucei brucei*.

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SYNTHESIS OF ALKALOID-LIKE COMPOUNDS WITH ALL-CARBON QUATERNARY CENTRES

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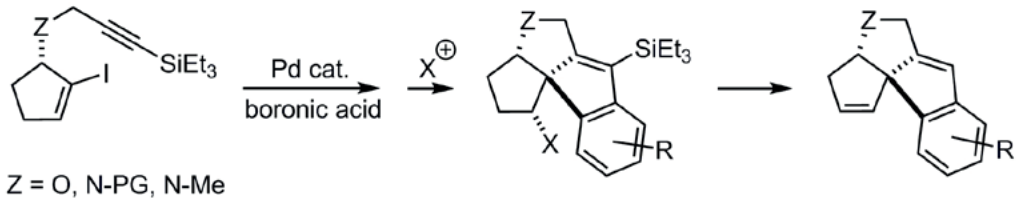
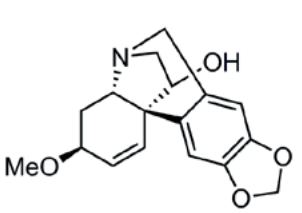
Recently, we have developed a method for the enantioselective synthesis of compounds containing all-carbon quaternary centres.[1] The two key transformations of this approach are tandem cyclisation/Suzuki cross-coupling and halocarbocyclisation.

In this work, application of the above-mentioned method in the synthesis of compounds with close structural similarity to alkaloids of *Amaryllidaceae* plant family is presented. Molecular dynamic simulation of these compounds was also performed, suggesting their binding activity to acetylcholinesterase.

Moreover, transformation of our products to important intermediates for the synthesis of haemanthamine or pretazettine derivatives is shown. These *Amaryllidaceae* alkaloids exhibit significant antiproliferative activity.[2,3]





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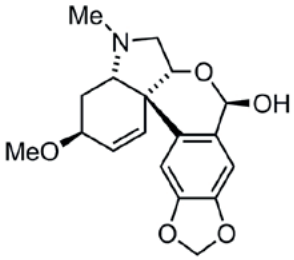

pretazettine

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NEW DUAL MOLECULES AS AN INNOVATIVE STRATEGY AGAINST GLIOBLASTOMA: SYNTHESIS AND BIOLOGICAL EVALUATION

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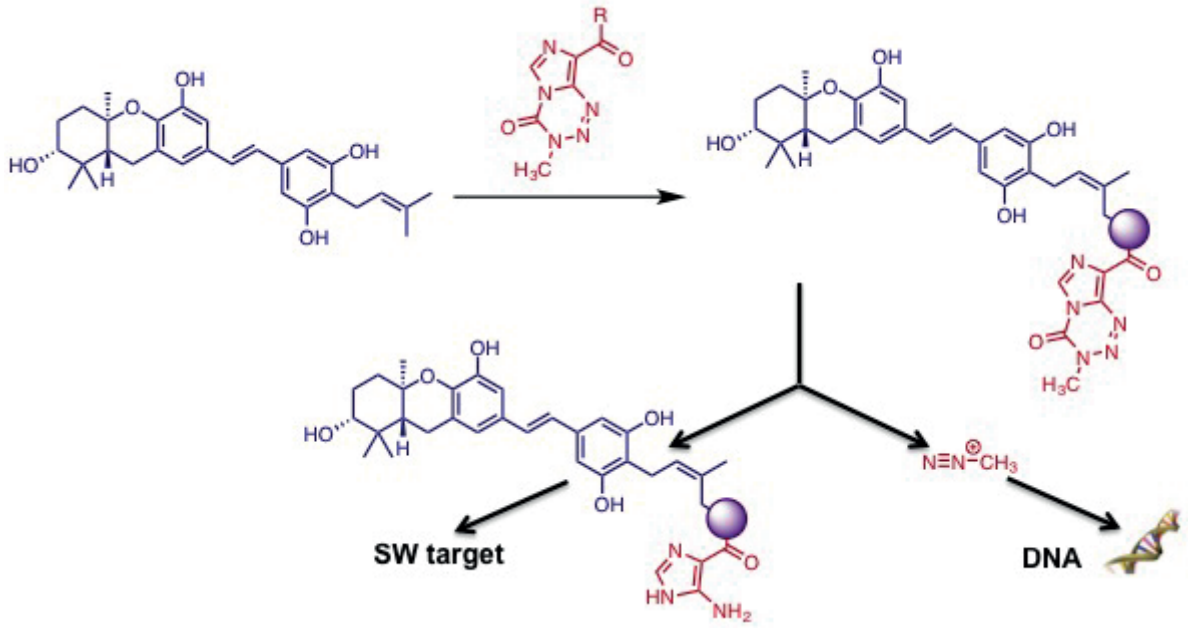
Glioblastoma multiforme (GBM) is by far the most malignant and common brain cancer, with a median length of survival of 15 to 18 months with treatment. The standard treatment consists in a combination of surgery, radiotherapy, and chemotherapy using temozolomide (TMZ), a DNA alkylating agent. However, this treatment only improves the median survival by three months, and some gliomas develop temozolomide resistance. Cho *et al.* have found that combining in a dual molecule TMZ and perillyl alcohol (POH), a natural compound that is active against glioblastoma, allows to increase the cytotoxicity against glioblastoma cells compared to POH alone, TMZ alone or the mixture of these two compounds.[1,2] This conjugated compound is also cytotoxic against TMZ-resistant glioblastoma cells.

Our team has isolated new cytotoxic compounds from *Macaranga tanarius* and *Macaranga vedeliana,* schweinfurthins (SW), that are highly active against glioblastoma cells, and they seem to be active on an other target than DNA.[3,4] Therefore, we synthesized new dual molecules combining schweinfurthin and temozolomide to study the activity of this new compound in the cell, and compared it with the schweinfurthin alone, the TMZ alone, and the mixture of SW and TMZ.



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SYNTHESIS OF HIGHLY SUBSTITUTED 1,3-OXAZINAN-2-ONE DERIVATIVES VIA MULTICOMPONENT REACTION

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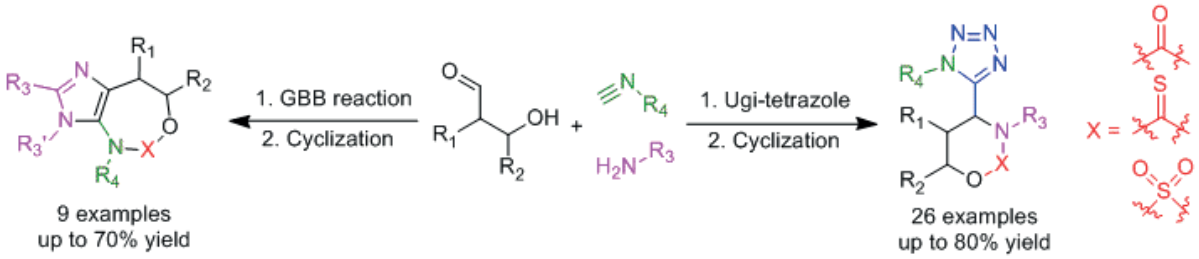
1,3-Oxazinan-2-one derivatives are highly potent heterocyclic compounds which do not only show remarkable biochemical activities as antibiotics, kinase inhibitors, HIV inhibitors in the development of drugs, but also play important roles in several chemical reactions as chiral auxiliaries.[1] There are many synthetic routes to obtain 1,3-oxazinan-2-ones. Most of them involve alkyl halide chemistry or require complex starting materials along with multiple steps. [23] However, these synthetic routes have several drawbacks such as harsh conditions, low yields as well as limited substitution pattern and diversity. Herein, we introduce a novel two-step synthesis of 1,3-oxazinan-2-one derivatives which have at least 4 substitutions with high yields utilizing multicomponent reactions followed by cyclization. A series of multi-substituted oxazolidinones, oxazinanones, oxazinanones as well as their thio- and sulfur- derivatives are synthesized from simple readily available building block with mild conditions and high yields, making this a very versatile scaffold synthesis strategy.



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STRUCTURE OF MEMBRANE BOUND PYROPHOSPHATASE FROM THERMOTOGA MARITIMA IN COMPLEX WITH IMIDODIPHOSPHATE AND N-[(2-AMINOBENZO[d]THIAZOL-6-YL)METHYL] -1H-INDOLE-2-CARBOXAMIDE

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Membrane bound pyrophosphatases (mPPases) are large homodimeric integral membrane proteins and can be found in human pathogens such as *Plasmodium* species (malaria).[1] These enzymes couple the hydrolysis of pyrophosphate (PP_i) to pumping of H^+ or Na^+ ions, generating an electrochemical potential across the acidocalcisomal membrane. This task is necessary for the parasites since PP_i, a by-product from many biosynthetic pathways, in too high concentrations may disturb physiological reactions. Although mPPases play an essential role for many pathogenic protozoan parasites they do not exist in humans, thereby making them promising drug targets.The first structure of a mPPase was solved in the Goldman laboratory.[2]

Our aim is to develop novel mPPase inhibitors capable of disrupting this key ion gradient of pathogenic protozoan parasites in order to decrease their viability. So far, mainly phosphorus-containing inhibitors of mPPases have been reported, limiting their therapeutic utility. However, through screening efforts of *Thermotoga maritima* PPase we found novel organic inhibitors. The best hit compound inhibited the enzyme activity uncompetitively with an IC_{50} of 1.7 μM.[3] The binding mode was solved by X-ray crystallography at 3.7 Å resolution together with the substrate analogue imidodiphosphate. The hit compound binds to the protein monomer near the exit channel, forming a hydrophobic clamp that locks the enzyme conformation in the closed state and thereby prevents hydrolysis and sodium pumping activity.

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STRUCTURE-ACTIVITY RELATIONSHIP-GUIDED SYNTHESIS AND IN VITRO CHARACTERIZATION OF GATA4 AND NKX2-5 PROTEIN-PROTEIN INTERACTION MODULATORS

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Cardiovascular disease is today the major cause of death and disease in developed as well as developing countries.[1] Heart failure alone affects more than 23 million people globally and imposes a huge economic burden for societies.[2] Cardiac transcription factors (TF), such as GATA4 and NKX2-5, regulate both physiological and pathophysiological processes in the heart. For example, a physical interaction of these two TFs is involved in stretch-induced cardiomyocyte hypertrophy. In our previous studies we have demonstrated that isoxazole hit compound inhibiting the GATA4-NKX2-5 transcriptional synergy attenuates cardiomyocyte hypertrophy in vitro[3] and improves cardiac function in vivo in experimental models of myocardial infarction and hypertension.[4]

In this work, we continued the optimization of the original isoxazole hit compound by synthesizing alternative northern, central and southern parts. The compounds were tested in the luciferase assay to examine the inhibition of the transcriptional synergy of the GATA4 and NKX2-5. Additionally, the most potent compounds were tested in luciferase assays for NKX2-5 and GATA4 activity individually. Furthermore, when cytotoxicity of the compounds was evaluated in MTT assay in the COS-1 cell line, it correlated with the inhibition of GATA4 activity. Finally, the most promising compounds were tested for antihypertrophic response in a cell-based assay by measuring BNP promoter activity in a rat neonatal cardiomyocytes.

In summary, we have synthesized and successfully identified inhibitors of GATA4 and NKX2-5 transcriptional synergy, which potently inhibit hypertrophic response in neonatal cardiomyocytes.

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APPROACH TO THE TOTAL SYNTHESIS OF GULMIRECIN B

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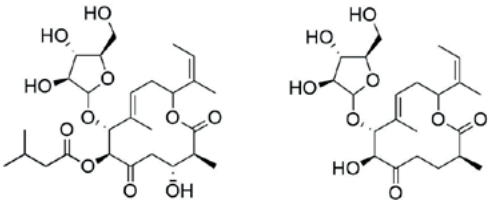
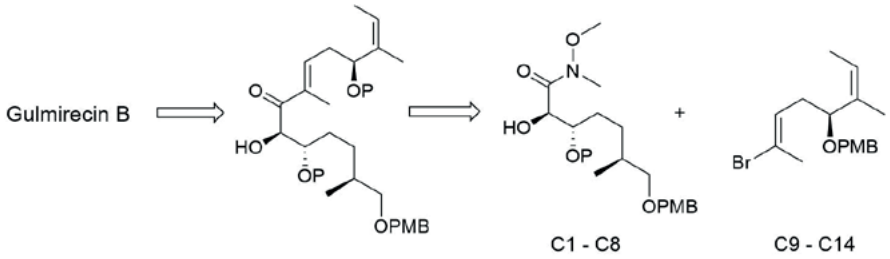
Multinational hospitals have had to deal with the number of resistant bacteria growing and evolving, leading to sickness and death caused by multiresistant bacteria.[1] The organic compounds Gulmirecin A and B were isolated by Nett et al. in 2013[2] with both substances demonstrating antimicrobial activity, especially against MRSA (Methicillin-resistant-stapphyloccocus aureus).[2]



The Gulmirecins are twelve-membered macrolactones with four stereocenters. Each macrocycle contains two alkene functions, therefore, they are interesting target molecules for a total synthesis.Up to this point there are two total synthesises published for the analog structures of disciformycin.[3][4] In Prof. Maiers working group, different approaches are investigated to build up the core structure of Gulmirecin B and recently the synthesis of the C1-C12 fragment was published.[5]



In our current approach, the macrolactone is constructed from two parts. A C1-C8 fragment and a C9-C14 fragment. The first fragments containing the C6-C7 diol originated from D-tartrate whereas the second part is synthesized from D-malic acid.

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STUDY OF THE 3-(PYRAZOL-4-YL)INDOLE PHARMACOPHORE FOR THE DEVELOPMENT OF NEW THERAPEUTIC AGENTS FOR CANCER TREATMENT

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Pyrazole and indole moieties have gained interest since the beginning and have been used as pharmacophores in drug discovery. These days, cancer is one of the main causes of deaths worldwide; thus there is an indispensable need to synthesize new drugs with intended anticancer activity. Very important compounds with such characteristics and properties, including indole or/ and pyrazole core in their main scaffold, are Doramapimod, Bisindole maleimides, Staurosporine, Meridianines, etc. These compounds, by interfering in complex biological signaling pathways, have the ability to inhibit proliferation, invasion, and metastasis in cancerous cells, but with the problems of toxicity and limited use, still remaining.

Our goal is the development of potent and selective inhibitors, based on these two interesting cores, which depending on their substitution and their physicochemical characteristics, will be specific for the treatment of different type of malignant diseases. Prompted by the above, here we describe the design and synthesis of several analogues of the above leads, including both pyrazole and indole scaffolds in their main scaffold. The new compounds showed significant anticancer activity against several cancer cell lines (WM2664 malignant metastatic melanoma)(less than 1 μM), T24 urinary bladder cell line) and a variety of molecular targets (TDP2, PIM1, CLK1, CLK4, and GSK3b kinases). According to SAR, and in silico studies, the new inhibitors, depending on the substitution of the 3-(pyrazol-4-yl)indole moiety, bind selectively in the active sites of the above enzymes (Figure 1).

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LATE-STAGE DIVERSIFICATION THROUGH MANGANESE-CATALYZED C–H Activation: ACCESS TO ACYCLIC, HYBRID, AND STAPLED PEPTIDES

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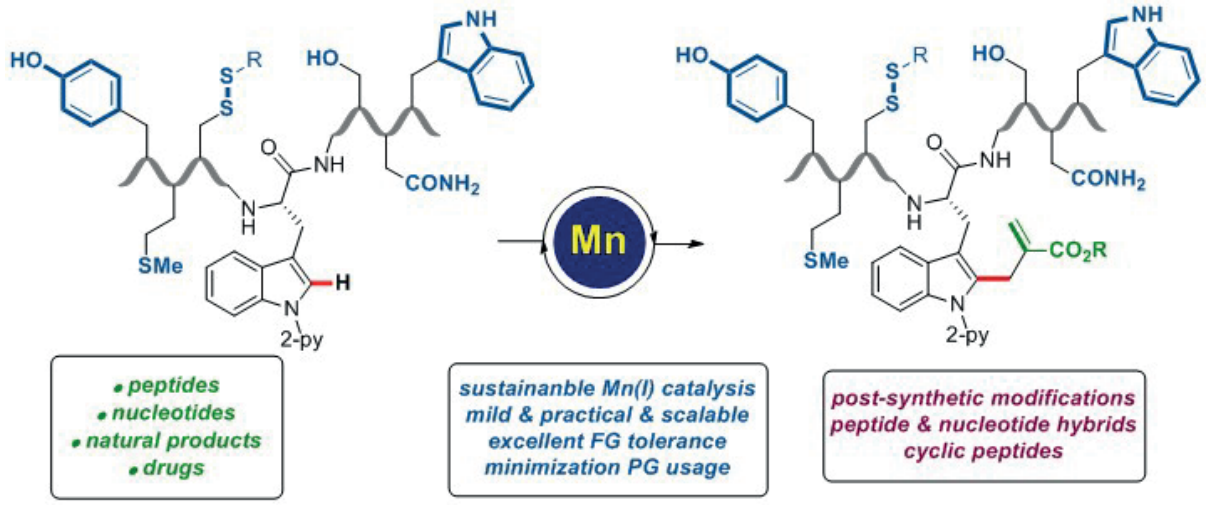
Non-natural peptides have emerged as increasingly potent scaffolds in medicinal chemistry and the pharmaceutical industry. As a consequence, the chemoselective assembly and modification of structurally complex peptides continues to be of utmost importance.[1] Significant recent momentum was gained through the development of palladium-catalyzed cross-couplings of peptides. A significantly more atom- and step-economic strategy relies on the direct activation of otherwise unreactive C–H bonds,[2,3] with recent transformative applications towards peptide modification.[5] As part of our program on sustainable C–H activation,[5,6] we reported on the first manganese-catalyzed C–H allylation of structurally complex peptides with easily accessible Morita–Baylis–Hillman adducts.[7] Notable features of our strategy include 1) an unprecedented manganese(I)-catalyzed peptide C–H alkylation, 2) the first metal-catalyzed peptide modification that installs synthetically useful α,β-unsaturated esters, 3) orthogonal late-stage diversification, and 4) a uniquely versatile manganese catalyst that proved applicable to C–H fusion with peptides, natural products, steroids, drug molecules, and nucleobases, among others.



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N-ALKYLATED SULFAMIDES AS NEUTRAL SOLUBILITY IMPROVING GROUPS FOR KINASE INHIBITORS

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Protein kinases are involved in various cellular processes such as proliferation, apoptosis, metabolism or intercellular communication. Hyperactivity of protein kinases can lead to inflammatory, neurological, immunological diseases or cancer [1]. One of the problems frequently encountered with protein kinase inhibitors is poor solubility, which hampers a straightforward preclinical development [2]. To optimize the aqueous solubility, various *N*-alkylated sulfamides were introduced as neutral solubility improving groups (NeuSIGs) into the structures of protein kinase inhibitors based on anilinoquinazoline or anilinopyrimidine scaffolds. Although adding molecular weight and molecular complexity, NeuSIGs are groups that are not increasing lipophilicity or stereocenters to the structure. Based on docking studies, the attachment points of the NeuSIGs were determined to ensure that the biological activity of the compounds was maintained despite their structural changes.

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NOVEL ACRIDINE DERIVATIVES AS TDP 1 AND/OR 2 INHIBITORS

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Cancer is a one of the most deadly diseases, responsible for about 13% of all deaths worldwide. It is normally caused by genetic abnormalities related to DNA of the affected cells; therefore, targeting the repair pathways of DNA could improve the efficacy of DNA-damaging anticancer drugs, such as clinically significant Topoisomerase-I (Top1) and Topoisomerase-II inhibitors. Among the most recently discovered DNA repair enzymes are Tyrosyl-DNA phosphodiesterases TDP1 and 2, which function is excising irreversible protein tyrosyl-DNA complexes involving topoisomerase 1 and/or 2 respectively. TDP1 catalyzes the hydrolysis of the phosphodiester bond between Top1 and DNA-3′-phosphate, suggesting a role in repairing of DNA double-strand breaks. Additionally, TDP2 removes many covalent adducts from DNA through hydrolysis of complexes between DNA and the Top2 active site tyrosine residue. TDP inhibitors reduce the destabilization and cleavage of stalled topoisomerase - DNA complexes, making them irreversible and thereby driving cancer cells into apoptosis.[1] Here, we describe the design, synthesis and pharmacological evaluation of novel amino substitutent tricyclic analogues as TDP1 and/or 2 inhibitors. The new compounds bear the the acridine or aza-acridine core, possessing one or two basic side chains. All compounds were tested for their activity against TDP1 and 2 and most of them showed significan activity. These results suggest in accordance with *In Silico* calculations, that the second basic side chain is essential for this activity, while also crucial is the presence of a methoxy substitution.

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INTERVENOLIN, A NOVEL ANTI-TUMOR DRUG, SUPPRESSES CANCER CELL GROWTH THROUGH MODULATION OF TUMOR MICROENVIRONMENT

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Tumor-stromal cell interactions are attractive targets for cancer chemotherapy and we have been focusing on small molecules modulating the interactions. Intervenolin (ITV), a novel natural compound, inhibits the growth of cancer cells in the presence of stromal cells (fibroblasts) more strongly than that in the absence of stromal cells. ITV exerts efficient anti-tumor activity in animal models without adverse effects. In this study we examined the mechanism of action of ITV. Since conditioned medium (CM) of stromal cells pretreated with ITV showed strong growth inhibitory effect against cancer cells, we then analyzed what factors could be dysregulated by ITV. As a result, we found that ITV increased the secretion of organic acids such as lactic acid and malic acid from stromal cells and changed the medium to be acidic. In that acidic condition we found that ITV suppressed the activity of p70 S6 kinase, a key enzyme in protein synthesis. Furthermore, concerning the secretion of lactic acid by ITV, we found that ITV inhibited mitochondrial complex I. These results suggest that ITV inhibits cancer growth though the modulation of microenvironment. Now we are studying whether the same phenomena occur in vivo.

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DISCOVERY OF A NOVEL NANOMOLAR SELECTIVE BUTYRYLCHOLINESTERASE INHIBITOR

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Recent studies have implicated butyrylcholinesterase (BChE) in late-stage Alzheimer's disease, prompting a shift in focus from acetylcholinesterase (AChE)-targeting inhibitors. Screening of an in-house library of benzimidazole analogs yielded a potent and selective nanomolar affinity BChE inhibitor coded BZD8A1 (eqBChE IC_{50} = 0.41 μM and BChE selectivity > 13-folds over eeAChE). Enzyme kinetics studies showed BZD8A1 to be a competitive inhibitor, with a K_i of 0.12 μM. Molecular docking analysis showed BZD8A1 occupying the space within the choline-binding site, oxyanion hole, acyl-binding site, and catalytic triad site of the enzyme. BZD8A1 did not show any significant toxicity against a panel of tested cell lines up to 50 uM, which was the highest concentration used. These values were more than 125-fold greater than the concentrations needed to achieve 50% in vitro inhibition of BChE. Evaluation of blood brain barrier (BBB) permeability and plasma stability identified BZD8A1 as having an optimal combination of high passive BBB permeability and high plasma stability.

NOVEL PYRROLO[2,3-d]PYRIMIDINE DERIVATIVES AS TRKA INHIBITOR WITH BROAD SPECTRUM ANTIPROLIFERATIVE ACTIVITY

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Tropomyosin receptor kinases (Trks) has been implicated in neurological disorders as well as neural and non-neural neoplasms. A new series of 5,6-disubstituted pyrrolo[2,3-d]pyrimidine octamides and their corresponding free amines have been synthesized and biologically evaluated for their antiproliferative activity against three human cancer cell lines. The 5,6-disubstituted octamides as well as the amine derivative have shown the best anticancer activity with single digit micromolar GI50 values over the tested cancer cells, and low cytotoxic effects (GI_{50}> 10.0 μM) against HFF-1 normal cell. Moreover, the most active member 6f was tested for its antiproliferative activity over a panel of 60 cancer cell lines at NCI, and exhibited distinct broad spectrum anticancer activity with submicromolar GI_{50} and TGI values over multiple cancer cells. Kinase profile of most active compound 6f over 53 oncogenic kinases at 10 μM showed its highly selective inhibitory activity towards FGFR4, Tie2 and TrkA kinases. The observed activity of 6f against TrkA (IC_{50} = 2.25 μM) was explained by molecular docking study, which also proposed that 6f may be a type III kinase inhibitor, binding to an allosteric site rather than kinase hinge region. Overall, compound 6f may serve as a promising anticancer lead compound that could be further optimized for development of potent anticancer agents.[1]

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ANALOGUES OF 5-SUBSTITUTED PYRIMIDINE NUCLEOSIDES AS ANTIMYCOBACTERIAL AGENTS

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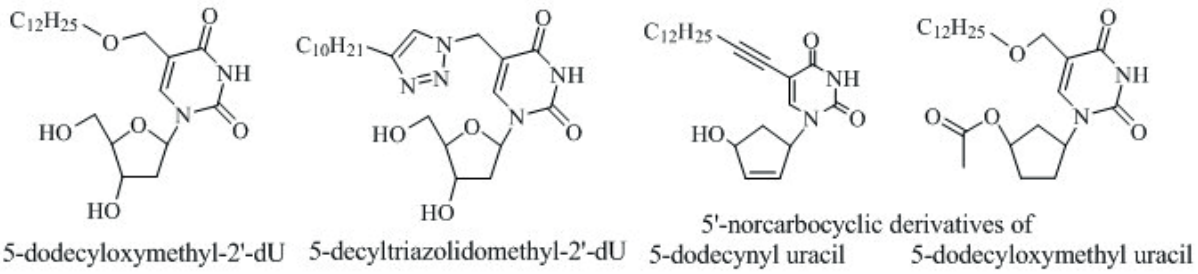
There are some reports on the modified nucleosides active against *M. tuberculosis*, *M. bovis* and *M. avium*.[1-3] The best activities among analogues of uridine (MIC_{90} 1-10 μg/ml) were found for 5-alkynyl (decynyl, dodecynyl, tetradecynyl, pyridylethynyl *etc.*) uracil derivatives bearing different sugar modification. 2'-Deoxypyrimidine derivatives with extended 5-alkyloxymethyl or 5-alkyltriazolidomethyl substituents (5-dodecyloxymethyl-2'-deoxyuridine, 5-decyltriazolidomethyl-2'-deoxyuridine, 5-dodecyltriazolidomethyl-2'-deoxycytidine etc.) showed ability to inhibit the growth of both laboratory H37Rv and clinical MDR MS-115 *M. tuberculosis* strains with MIC_{99} about 10 μg/mL.[4] Two groups of carbocyclic nucleoside analogues, namely 5'-norcarbocyclic derivatives of 5-alkynyl uracil and 5-alkoxymethyl uracil also showed antimycobacterial activity against H37Rv and MDR MS-115 strains of *M. tuberculosis*.[5,6] Unfortunately the mechanisms of 5-substituted pyrimidine nucleosides analogues action and target enzymes still are unclear.[1,2,4-6]



The data of transmission electron microscopy (TEM) evaluation of *M. tuberculosis* H37Rv bacterial cells treated with four lead compounds, one from the each groups described above, will be presented. We have found destruction of the bacterial cell wall, suggesting that the mechanism of action for these compounds may be related to their interactions with bacteria cell walls.

Acknowlegements

The work was supported by Russian Science Foundation, project № 18-29-08010.

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METHYLATED SPERMIDINE ANALOGS: SYNTHESIS AND INTERACTION WITH THE ENZYMES OF POLYAMINE METABOLISM

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The biogenic polyamines, spermidine (1,8-diamino-4-azaoctane, Spd) and spermine (1,12-diamino-4,9-diazadodecane, Spm) are ubiquitous organic polycations present in all eukaryotic cells in μM-mM concentrations and involved in the regulation of numerous vital processes including the differentiation and growth of cells [1]. High intracellular concentration of Spm and Spd *a priori* determines the multiplicity of their cellular functions. Studies of individual cellular functions of Spm and Spd are complicated by partial interchangeability of Spm and Spd and ease of their interconversion. Disturbances of polyamines metabolism are associated with the development of many diseases, including malignant tumors, decreased immune response, some types of pancreatitis, Snyder-Robinson's syndrome, and even type 2 diabetes [1]. Biological evaluation of rationally designed polyamine analogs is one of the cornerstones of polyamine research having obvious basic and practical values. Here we synthesized and characterized *C*-methylated Spd analogues possessing a biochemically useful set of properties.

The synthesis of title compounds was performed starting from amino alcohols by subsequent elongation of polyamine backbone [2,3]. Obtained data demonstrate that the biochemical properties of *C*-methylated polyamine analogs can be regulated by changing the position of the methyl substituent, and at more precise level by changing the configuration of chiral center [2,4,5]. Hidden stereospecificity (natural substrates are achiral) was shown for the enzymes of polyamine metabolism using title compounds [2,4,5]. The first metabolically stable functionally active mimetic of Spd, i.e. (*R*)-1,8-diamino-3-methyl-4-azaoctane, being suitable for the investigation of the individual cellular functions of partly interchangeable and easily interconvertible Spm and Spd was found [4].

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ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF 2,4-DIARYL-1-BENZOPYRANS VIA DECARBOXYLATIVE ALKYLATION OF β-KETO ACIDS TO o-QUINONE METHIDES

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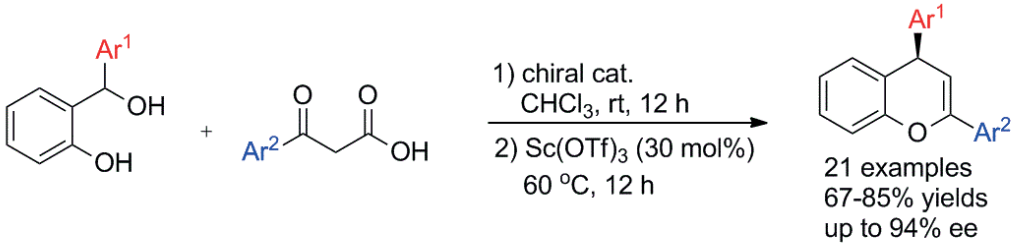
4*H*-1-Benzopyrans are a privileged class of structural motifs found in many pharmaceuticals and bioactive natural products.[1] In particular, 2,4-diaryl-1-benzopyrans bearing a stereogenic center at the C_4-position have been reported to be biologically active against a variety of targets. Consequently, the asymmetric synthesis of 2,4-diaryl-1-benzopyran derivatives has received significant attention as a research area in organic chemistry over the past decades. In connection with ongoing research program on the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[2] we recently reported catalytic enantioselective C–C bond formations of active methylenes and methines.[3] In this presentation, a novel and efficient asymmetric synthesis of 2,4-diaryl-1-benzopyrans via enantioselective decarboxylative alkylation of β-keto acids to o-quinone methide intermediates, followed by sequential cyclization and dehydration has been developed.[4] The synthetically useful chiral 2,4-diaryl-1-benzopyran derivatives were obtained in moderate to high yields and high enantioselectivities through a one-pot, two-step sequence. This approach offers a facile way to prepare chiral 2,4-diaryl-1-benzopyran derivatives with a wide range of functional group tolerance.



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PEPTIDOMIMETIC PLASMEPSIN INHIBITORS WITH POTENT ANTI-MALARIAL ACTIVITY AND SELECTIVITY AGAINST CATHEPSIN D

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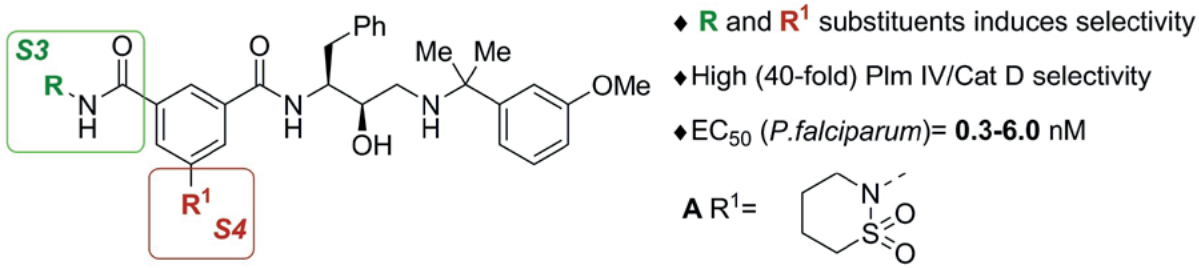
Malaria is a life-threatening disease caused by *Plasmodium* parasites which are transmitted by mosquites.[1] The spread of drug-resistant malaria parasites urges the development of new antimalarial drugs. Malarial aspartic proteases – plasmepsins (Plm I, Plm II, Plm IV, HAP) – are found in the food vacuole of the parasite. The plasmepsins are involved in processing of hemoglobin to amino acids and are considered as attractive drug targets.[2]

Hydroxyethylamine derivative **A** was recently published by *GlaxoSmithKline* as potent antimalarial which shows high inhibitory activity against Plm IV but no selectivity *versus* human aspartic protease Cathepsin D (CatD).[3] For the lead optimization Plm IV was used as a readily accessible model protein, the inhibition of which was previously found to correlate with results of parasite growth assay. Based on sequence alignment of Plm IV and Cat D, the selectivity factor (S) Plm IV/Cat D of antimalarial hit **A** was optimizied by changing substituents occupying *S3* and *S4* sub-pockets.[4]



Introduction of an *S3* sub-pocket targeting mono-substituted amide moiety containing linear or branched hydrophobic groups resulted in up to 40-fold Plm IV/Cat D selectivity factor. Plm IV inhibitors with no substituents or fluorine targeting the *S4* sub-pocket led to 20-fold selectivity against Cat D. Determination of parasite growth inhibition potency for selected Plm inhibitors showed activities in the low nano-molar range (0.3-0.6 nM).[4]

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DESIGN, SYNTHESIS AND EVALUATION OF MICRONEUROTROPHINS, NOVEL SYNTHETIC AGONISTS OF NEUROTROPHIN RECEPTORS

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Neuronal cell death by apoptosis is the "end point" of many human neurological disorders, including Alzheimer's, Parkinson's, and Huntington's diseases, stroke/trauma, amyotrophic lateral sclerosis and ocular pathologies as glaucoma, retinitis pigmentosa, diabetic retinopathy and age-related macular degenaration. Neurotrophins control neuronal cell fate and function acting through two classes of cell surface receptors, the Trk family of receptor tyrosine kinases and the $p75^{NTR}$, a member of the tumour necrosis factor receptor superfamily. The neurotrophin NGF sends its survival signals through activation of TrkA and can induce death by binding to $p75^{NTR}$.[1] Its therapeutic usefulness though is compromised by its polypeptidic nature and limited penetrance to the blood-brain barrier (BBB).

Based on our previous studies, BNN27 an analog of the neurosteroid dehydroepiandrosterone featuring a 17-spiro epoxy moiety, has been shown to bind specifically the NGF receptors TrkA and $p75^{NTR}$ at nanomolar concentrations (Kd: 1.86±0.4nM and 3.9±1.2nM respectively). Upon binding BNN27 induces down-stream neuronal survival-related TrkA signaling and controls specific $p75^{NTR}$-mediated signaling of neuronal cell fate. *In vitro* experiments have shown that BNN27 effectively rescues from apoptosis NGF dependent and TrkA positive sympathetic and sensory neurons and *in vivo* studies evidence that BNN27 synergizes with NGF in promoting axonal outgrowth and effectively rescued NGF-dependent and TrkA-positive sympathetic and sensory neurons from apoptosis, *in vitro*, *ex vivo* and *in vivo* in NGF-KO mice. The efficacy of synthetic microneurotrophins in protecting neurons from apoptosis was tested in various experimental animal models of neurodegenerative diseases with excellent results. Biomolecular STD-NMR and *in silico* studies have provided evidence for the potential hot spots of interaction of BNN27 at the neurotrophin receptors and their complexed forms with NGF.[2-4]

In the context of our ongoing efforts for microneurotrophins development we have conducted a lead optimization phase comprising a steroidal focused library with analogs bearing structural modifications at the 17 position of the steroidal core, which led to the more potent lead compound BNN237. The design was guided by the increase of the van der Waals interactions in the predicted binding sites and the improvement of the pharmacokinetic profile i.e. lipophilicity tuning, optimized BBB membrane permeability, metabolic stability.

Microneurotrophins BNN27 and BNN237 are lead molecules for the development of neurotrophin receptor modulators, with potential therapeutic applications in neurodegenerative diseases, brain trauma and neuropathic pain.

Acknowledgement

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4) WO2008GB02067 20080617, "Neurosteroid Compounds"

HECK REACTION OF CYCLOPROPANATED PYRROLES - SYNTHESIS OF NOVEL NIPECOTIC ACID DERIVATIVES

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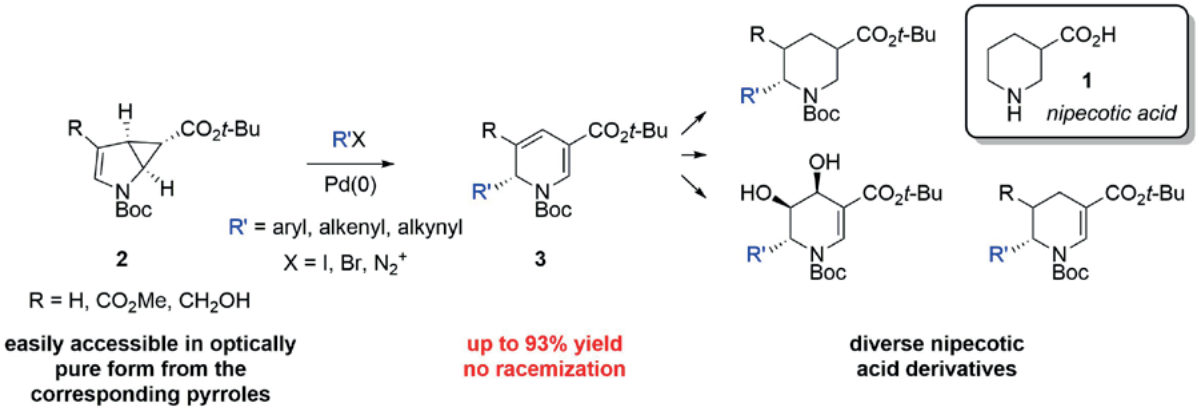
Piperidine-based amino acids receive much research interest due to interesting structural and biological features of their peptides [1]. Therefore, new methods for the asymmetric synthesis of these heterocycles are highly desirable.

Recently, our group developed a strategy for the preparation of highly functionalized derivatives of nipecotic acid **1** which is based on Heck coupling of cyclopropanated pyrroles **2** [2]. The reaction proceeds with good yields with a variety of coupling partners and importantly without racemization. The resulting products, 1,2-dihydropyridine-3-carboxylates **3**, constitute versatile synthetic intermediates, which was demonstrated by a number of further transformations.



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EXPLORING THE CHEMICAL SPACE ECONOMICALLY

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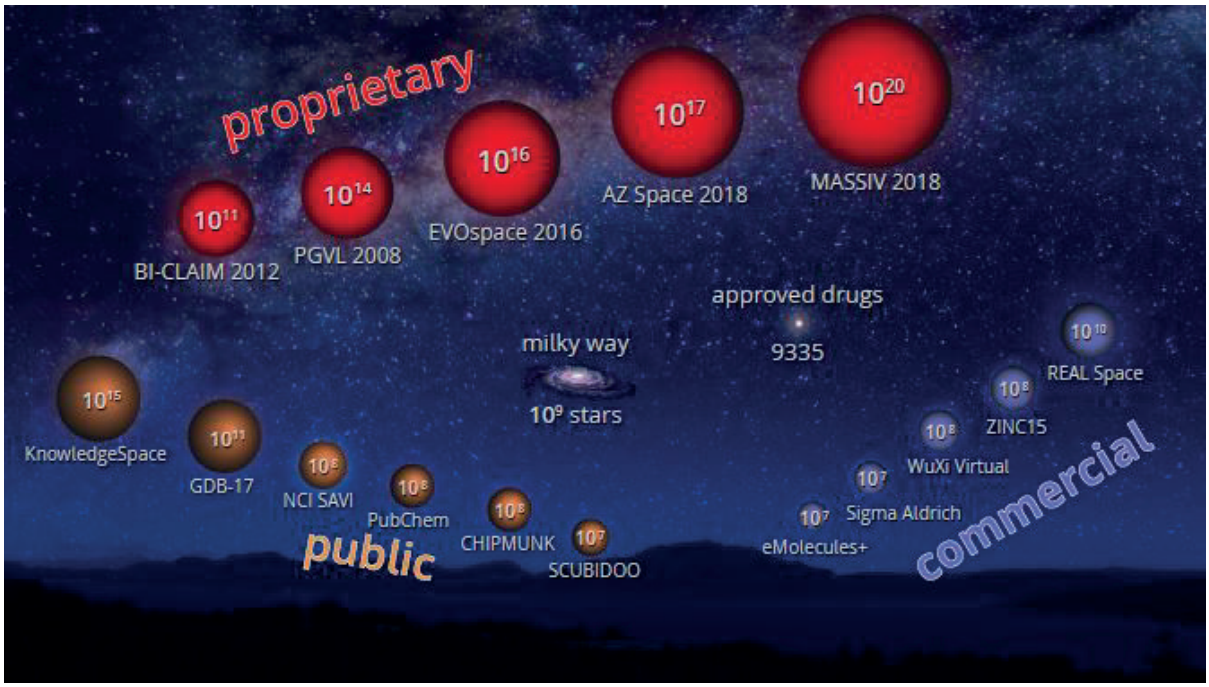
De novo proposals from computer programs that search through large chemical collections ("spaces") is experiencing a huge come-back these days.
While in the past, the medicinal chemists' acceptance of computer-generated proposals has often been lacking, it has been realized that any computer-based de novo proposal must take synthetic access into account intelligently. Such "next-generation" chemical spaces are spun up by combinatorial reaction knowledge. Navigating these vast molecular resources corresponds to searching in tens of billions of molecules of previously inaccessible molecular entities. The new space concepts have been applied to various corporate / in-house, reaction-driven spaces, the largest of which today reach sizes of 10^{20}.
Searching in such large amounts of data using traditional methods that are based on enumeratied molecule collections is prohibitive with such amount of data. However, due to their combinatorial nature, the navigation of the reaction-driven spaces can be accomplished much faster than with traditional approaches. It uses pharmacophore-inspired similarity searches to given query compounds; tree-based algorithms deliver nearest neighbors within minutes on standard hardware.
As the first chemical space of readily deliverable ("tangible") compounds the Enamine REAL Space has recently surpassed the 11 billion barrier. Using easy-to-use software, medicinal chemists can now execute rapid scaffold-hopping experiments, fast hit expansion, and structure-activity-relationship (SAR) exploitation in largely intellectual property (IP)-free territory. We will outline the rationales, give examples, report on feedback from users, and assess success and delivery rates.



NOVEL BENZAMIDES EXHIBITING POTENT CYTOTOXIC ACTIVITY AGAINST CANCER CELL LINES

Dimitrios-Triantafyllos Gerokonstantis (1), Alexandros C. Kokotos (2), Christiana Mantzourani (1), Aikaterini Nikolaou (1), Alexandra Zambouli (1), Dimitrios Gkikas (2), Panagiotis K. Politis (2), Panagiota Moutevelis-Minakakis (1), George Kokotos (1)

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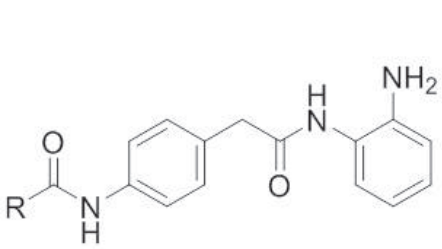
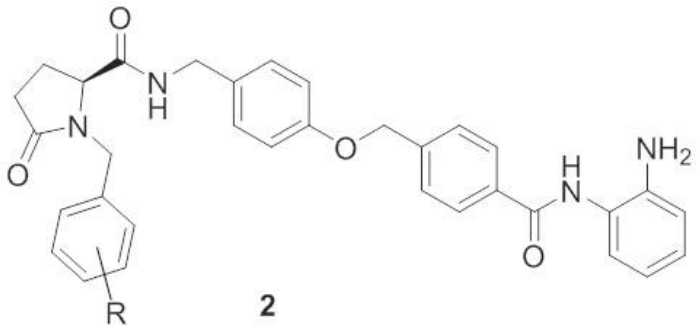
Histone deacetylases (HDACs) have recently attracted special interest, because their inhibitors may find applications for the treatment of cancer, neurological diseases and immune disorders [1]. Hydroxamates vorinostat, belinostat and panobinostat have been approved for use in cutaneous T-cell lymphoma, peripheral T-cell lymphoma, and multiple myeloma, respectively, while the benzamide chidamide [2] for peripheral T-cell lymphoma. A few additional benzamides (entinostat, mocetinostat, tacedinaline) are currently under clinical trials. In this work, we present the synthesis of various novel amino anilides and benzamides and the evaluation of their cytotoxic activity against various cancer cell lines.

Amino anilides of general structure **1**, containing either medium and long chains or chains bearing an aromatic ring at the terminus, were synthesized using 4-aminophenylacetic acid as a starting material. Benzamides of general structure **2** were based on either L- or D-pyroglutamic acid and a variety of substituents were studied on the N-benzyl functionality. The in vitro cytotoxic activities of the compounds synthesized were studied against diverse cancer cell lines (A549, Caco-2, SF268) applying the MTT viability assay. Novel benzamides displaying potent anti-proliferative activity with IC_{50}s ranging from 2 to 10 μM were identified.



1, R= alkyl, aralkyl



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A LIPIDOMICS-BASED LC-HRMS METHOD FOR MONITORING THE FATTY ACID LEVELS IN CELLS AFTER TREATMENT WITH ENZYME INHIBITORS

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Phospholipases A_2 (PLA_2s) are considered as a key-player in inflammatory diseases and as a consequence, a variety of synthetic inhibitors of PLA_2s have been developed during the last two decades as potential new medicinal agents [1]. PLA_2s catalyze the hydrolysis of glycerophospholipids releasing free fatty acids and each group of PLA_2s presents different substrate specificity [2]. Among the various PLA_2s, cytosolic GIVA $cPLA_2$ shows a marked preference for hydrolysis of arachidonic acid from the *sn*-2 position of membrane glycerophospholipids, initiating the arachidonic acid cascade. It is of great importance to monitor the changes in the release of free fatty acids caused by an enzyme inhibitor in a cellular environment. We describe here a lipidomics-based LC-HRMS method for the determination of the levels of free fatty acids in cells after treatment with a PLA_2 inhibitor.

For the LC/HRMS studies, an AB SCIEX TripleTOF® 4600 system, a micro-LC Eksigent and an autosampler were used. Electrospray ionization (ESI) –negative ion mode– was used for the Full Scan MS experiments. Halo C18 2.7 μm 90Å 0.5x50 mm from Eksigent was used as a column and the mobile phase consisted of a gradient (A: acetonitrile/0.01% formic acid-isopropanol 80/20 v/v; B: H_2O/ 0.01% formic acid). The data acquisition was carried out with MultiQuant™ from AB SCIEX (version 3.0).

The method allows the simultaneous determination of twenty two medium and long chain saturated and unsaturated fatty acids in a 10-min run. SHSY5Y cells were treated in the absence or presence of the 2-oxoester GIVA $cPLA_2$ inhibitor GK200 [3]. An interesting decrease of arachidonic acid was observed confirming the effect of inhibitor GK200 in SHSY5Y cells. In addition, a decrease in the levels of adrenic acid was measured. The method described herein may find general applications for the determination of free fatty acid levels in cells after treatment with an enzyme inhibitor.

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MAPPING THE ACTIVE STATE OF A3 ADENOSINE RECEPTOR USING A COMBINATION OF MOLECULAR DYNAMICS SIMULATIONS, MM-GBSA CALCULATIONS AND MUTAGENESIS

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A_3AR is over-expressed in various tumor cells, compared to normal cells where it was found having low or no expression. Thus, A_3AR and its signaling pathway is a promising drug target against cancer cell proliferation and for a number of other conditions like inflammatory diseases, including asthma and rheumatoid arthritis, and ischemic injury. Currently there is no crystallographic structure for A_3AR and in this work the orthosteric binding site of the active state A_3AR in complex with two agonists, the selective IB-MECA (**4**) and the non-selective NECA (**3**) was studied. Molecular dynamics simulations (MD) and Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) free energy calculations of WT and mutant A_3ARs in complex with **3** or **4** were performed in combination with several site-directed mutagenesis studies, and biological data from functional assays to validate the *in silico* predictions. For the new residues tested it was found that mutations (a) $V169^{5.30}A$, $I249^{6.54}A$, $I253^{6.58}A$ increase the activity of at least one agonist, (b) mutations $L90^{3.32}A$, $M174^{5.35}A$ reduce the activity of at least one agonist, (c) mutations $F168^{5.29}A$, $L246^{6.51}A$, $I268^{7.39}A$ $T94^{3.36}A$, $M177^{5.38}A$, $N250^{6.55}A$, $S271^{7.42}A$, $H272^{7.43}A$ negate agonist activity and (d) mutations $W185^{5.46}A$, $I253^{6.58}A$, $L264^{7.35}A$ have no effect on agonist activity and do not participate on receptor activation. The results contributed significantly to the definition of the orthosteric binding area.

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A STRATEGIC APPROACH TO HIT IDENTIFICATION FOR POTENTIAL SUBSTRATE REDUCTION THERAPY OF MUCOPOLYSACCHARIDOSIS

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Mucopolysaccharidosis (MPS) is a group of lysosomal storage disorders (LSDs) caused by the overstocked and accumulated molecules known as glycosaminoglycans (GAGs) as a result of dysfunction and absence of lysosomal molecules that can degrade GAGs. Sugar transferases have a crucial role in the control and are potential therapeutic targets of MPS substrate reduction therapy (SRT), and therefore finding an inhibitor has an excellent opportunity to discover a new drug of MPS disease area. To prepare an MPS disease model cell line, CRISPR-Cas9 was used to knock out the gene which is related to the degradation of GAG, and the model cell line was confirmed by sequencing, ELISA, and GAG synthesis levels. In this disease model cell line, various sugar transferase genes were knocked out to identify druggable target protein, resulting in three targets. Among them, target A protein showed the highest druggability potential in cell phenotype observation. Hit screening strategy against target A is now in progress through a combination of two different hit finding approaches, high throughput screening (HTS) and fragment-based drug discovery (FBDD).

THE IMPACT OF INFLUENZA A M2 TRANSMEMBRANE DOMAIN AND ADAMANTANE-BASED LIGANDS ON PROPERTIES OF DMPC BILAYERS: DSC, ssNMR SPECTROSCOPY, X-RAY SCATTERING, AND MD SIMULATIONS

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The effects in dimyristoylphosphatidylcholine (DMPC) bilayers of including the influenza A M2 protein transmembrane domain (M2TM) with or without an six-fold excess of amantadine (*Amt*) or the synthetic analog spiro[pyrrolidine-2,2′-adamantane] (*AK13*) were studied using differential scanning calorimetry (DSC), small- and wide-angle x-ray scattering (SAXS and WAXS), solid state NMR (ssNMR) and molecular dynamics (MD) simulations. The influence of the M2TM on the DMPC bilayers without or with drug was evaluated by DSC and SAXS. At low peptide concentrations, two lipid domains were observed that likely correspond to the M2TM boundary lipids and the bulk-like lipids. At high peptide concentrations, one domain was identified which constitute essentially all of the lipids which behave as boundary lipids. MD simulations, and ^{1}H, ^{31}P ssNMR showed that M2TM in apo form or drug-bound form span the membrane interacting strongly with lipid acyl chain tails and the phosphate groups of the polar head surface. The ^{13}C ssNMR experiments allow the inspection of excess drug molecules and the assessment of its impact on the lipid head-group region. The MD simulations showed that the drugs anchor through their ammonium group with the lipid phosphate and occasionally with M2TM asparagine-44 carboxylate groups. According to SAXS, WAXS and DSC, in the absence of M2TM both drugs exerted a similar perturbing effect on the bilayer at low concentrations. Interestingly, at the same concentrations when M2TM is present, the *Amt* and, to a lesser extent, *AK13* caused a significant disordering of chain stacking. This effect is likely to the stronger ionic interactions of *Amt* primary ammonium group with phosphate groups, compared with the secondary buried ammonium group in *AK13*, and to the preference of *AK13* to locate in closer vicinity to M2TM compared to *Amt*.

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RECENT ADVANCES IN HETEROCYCLIC SYNTHESIS VIA MULTI-COMPONENT REACTION SCHEMES

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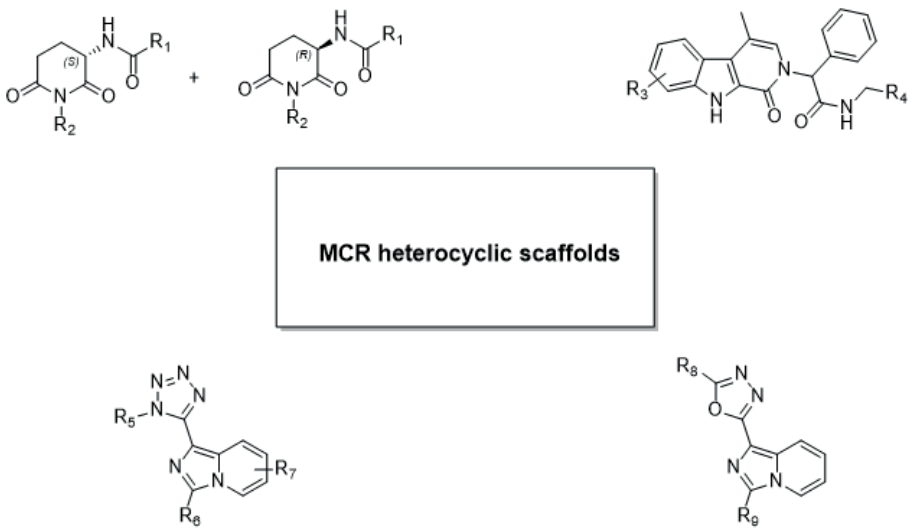
Heterocycles are the cycles mostly used in drug discovery. New, elegant synthetic routes towards heterocycles are still of high demand in order to shorten reaction schemes, simplify synthetic routes and in some cases discover greener approaches with high atom economy. Most of the these requirements are fulfilled by multi-component reaction chemistry (MCR),[1]which in contrast to traditional step-wise synthesis, allows the synthesis of complex structures in a few synthetic steps, starting from commercially available or easily accessible starting materials.



Here, we present synthetic methodologies based on MCR chemistry that significantly accelerate the library synthesis of natural product analogues, especially for the scaffolds of glutarimide alkaloids[2] and beta-carbolinones.[3] Moreover, sequential reactions, starting from an Ugi-tetrazole reaction were established for the library synthesis of imidazo[1,5- a]pyridines bis-heterocycles bearing either a tetrazole[4] or an oxadiazole[5] motif. Both bis-heterocyclic scaffolds, have applications in medicinal chemistry, material science and fluorescent probes.

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DEVELOPMENT OF ALLOSTERIC INHIBITORS OF ColH USING DCC STRATEGY

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The growing number of antibiotic-resistant bacteria represents one of the biggest risks to public health, leading to rapid emergence of infections that are impossible to treat.[1] Therefore, there is an urgent need for discovering novel targets and antibiotics with novel mechanisms of action. Due to the arising problem of antibiotic resistance, particular emphasis has been put on targeting bacterial virulence as an alternative approach for fighting microbial infections.[2] The resulting anti-virulence agents will preserve the commensal microbiome and are expected to be less prone to the development of resistance than conventional antibiotics. The Gram-positive bacterium *Clostridium histolyticum* is responsible for high mortality rates worldwide. It produces collagenase ColH as a virulence factor, an attractive target for the treatment of *C. histolyticum*-derived infections.[3]

The main problem with protease inhibitors is their lack of stability under physiological conditions, as well as their lack of selectivity towards human matrix metalloproteases (MMPs), which makes them unsuitable candidates for antibacterial treatment in *in vivo* models. In our work, we aim to discover allosteric inhibitors of ColH, which do not have to contain a zinc-binding motif. To reach this goal, we are using dynamic-combinatorial chemistry strategy (DCC), a powerful tool that accelerates drug discovery in its early stages to a significant extent.[4,5,6] The overall idea is to block the active site of ColH with a known inhibitor and to screen the resulting complex against a dynamic combinatorial library (DCL). This results in shifting of the equilibrium and leads to selection and amplification of the strongest allosteric binders (Figure 1). Among various reactions that can be performed using this method, we selected the acylhydrazone formation. The reaction is performed in acetate buffer (pH=5), as by using the thermal shift assay we observed the protein to be stable under these conditions. In each DCC experiment, we use approximately 2–3 aldehydes and 8–12 hydrazides (Figure 2). Experiments are analyzed by using a liquid chromatography-mass spectrometry technique (LC-MS), which allows separation of complex mixtures of possible products, as well as assignment of compounds by their mass.

Figure 1. Novel DCC approach for discovering allosteric inhibitors of ColH

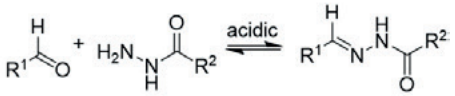

Figure 2. Reversible reaction to be used in protein-templated DCC

By using this strategy, we obtained several hits with amplification up to 800%. These hits were synthesized and will be further examined for their potency against ColH. Having these results in hand, we will thoroughly modify the structures of the initial hits to obtain more potent inhibitors. This will represent the first application of DCC for the discovery of novel inhibitors of ColH and for allosteric inhibitors in general.

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ENCAPSULATION OF NARINGIN IN BIODEGRADABLE CARRIERS

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Flavonoids are natural products, which comprise a large group of polyphenolic compounds and secondary metabolites, while they also consist a source of bioactive compounds in plants. Their importance is also significant for human health due to their exceptional ability to act as radical scavengers. Naringin is a flavanone 7-O-glycoside and is a basic ingredient in citrus fruits, mainly in grapefruit. It possesses numerous biological and pharmacological properties including antioxidant, anti-allergic, anti-inflammatory, antiviral, cardiovascular, hypolipidemic, neuroprotective, hepatoprotective and anticancer activities[1].

Encapsulation of bioactive compounds in polymeric nanoparticles has tremendous potential, as it can improve the physicochemical characteristics of the ingredients thus enhancing penetration for better efficacy, help target specific cells thus resulting in improved drug delivery, controlled release as well as protection of unstable, sensitive or volatile compounds. Nanoencapsulation has been extensively studied in Medicine, Pharmaceutical and Cosmetics fields. Poly (lactic acid) (PLA) is a widely used, FDA approved biocompatible, biodegradable and bio-based polymer which finds numerous applications as a drug carrier[2,3]. Another popular biocompatible carrier is chitosan, a hydrophilic natural polysaccharide that swells when dispersed in water and can adhere to the surface of negatively charged nanoparticles. Chitosan has attracted great deal of interest for medical, pharmaceutical and agricultural applications, due to its biodegradability, biocompatibility, nontoxicity, antibacterial and antiviral properties. Recent trends show that new or improved properties of chitosan could be obtained through its chemical modification, attaching various functional groups to its amino or hydroxyl groups[4]

The present work focuses on the study of the encapsulation of naringin in poly (lactic acid) (PLA) nanoparticles, as well as on the formation of PLA nanoparticles coated with chitosan or chemically modified chitosan. The encapsulation in PLA is succeeded via the emulsification – solvent evaporation technique as the method of preparing all the particles. Furthermore, several chemically modified chitosan derivatives are synthesized, like amides or imines, while all final products are fully characterized.

Size, polydispersity index and ζ-potential determinations of encapsulated nanoparticles were performed by Dynamic Light Scattering (DLS). The positive value of ζ-potential in the coating of the nanoparticles is attributed to the presence of chitosan and it consists an evidence of the successful modification. DSC and TGA (Thermogravimetric Analysis) analysis was carried out for the characterization of the thermal properties of the nanosystems, as well as in order to assess the drug-polymer compatibility and miscibility. FT-IR and NMR spectroscopy were used to study the structure of the nanoparticles.

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DESIGN, SYNTHESIS AND EVALUATION OF NOVEL 2,4-BISUBSTITUTED ARYLTHIAZOLES AS TRYPANOCIDALS

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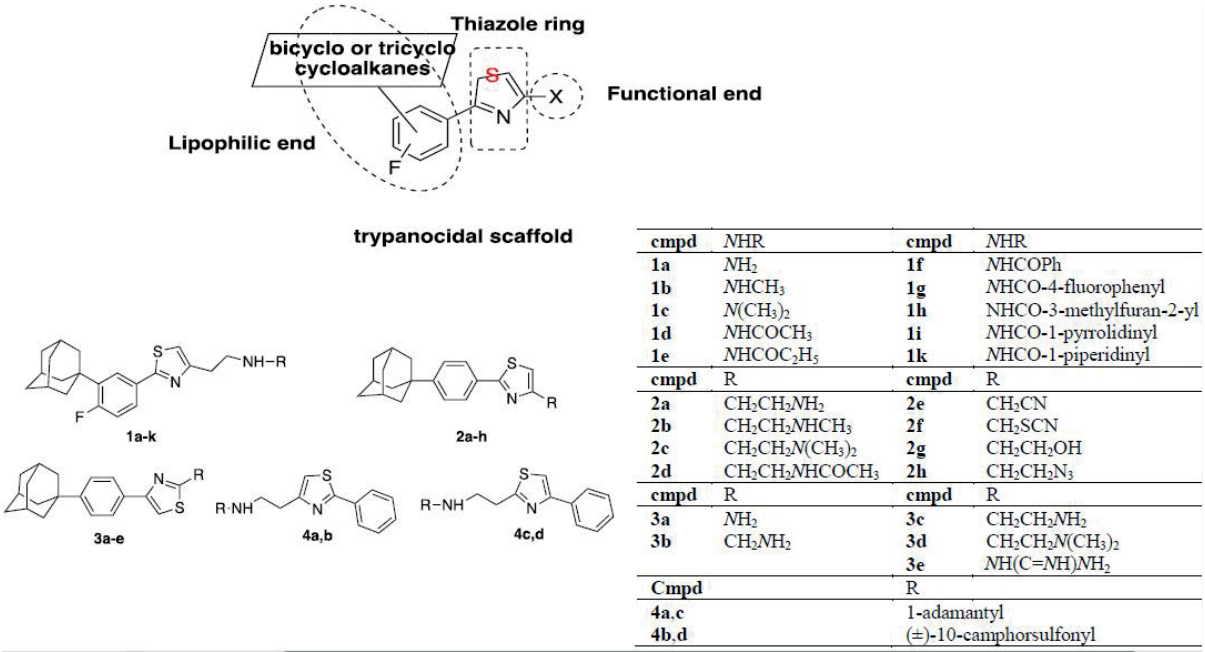
Trypanosomiases, as all NTDs, have lost their endemicity because of the globalization of economy, human and capital translocation, as well as, vector and host transportation. New drugs are required to treat trypanosomiases, as those currently available are characterized as out-of-date with severe side-effects and mounting parasite resistance.

We have been interested in adamantane chemistry and have prepared a large number of analogues in an attempt to exploit adamantane's role in bioactivity[1-3]. In the context of this research, we report herein on the design, synthesis and pharmacological evaluation of the 4-sybstituted-2[3-(adamant-1-yl)-4-fluorophenyl]thiazoles **1a**-**k,** the 4-substituted-2[4-(adamant-1-yl)phenyl]thiazoles **2a**-**h**, the 2-substituted-4[4-(adamant-1-yl)phenyl]thiazoles **3a**-**e**, the *N*-substituted 2-phenylthiazol-4-ethylamides **4a**,**b**, and the *N*-substituted 4-phenylthiazol-2-ethylamides **4c**,**d**. Analogues **1b** and **2b** exhibit a noteworthy trypanocidal activity, in the range of IC_{50}=0.59 to 0.90 μM.



cmpd	*N*HR	cmpd	*N*HR
1a	NH_2	**1f**	*N*HCOPh
1b	$NHCH_3$	**1g**	*N*HCO-4-fluorophenyl
1c	$N(CH_3)_2$	**1h**	NHCO-3-methylfuran-2-yl
1d	$NHCOCH_3$	**1i**	*N*HCO-1-pyrrolidinyl
1e	$NHCOC_2H_5$	**1k**	*N*HCO-1-piperidinyl
cmpd	R	**cmpd**	R
2a	$CH_2CH_2NH_2$	**2e**	CH_2CN
2b	$CH_2CH_2NHCH_3$	**2f**	CH_2SCN
2c	$CH_2CH_2N(CH_3)_2$	**2g**	CH_2CH_2OH
2d	$CH_2CH_2NHCOCH_3$	**2h**	$CH_2CH_2N_3$
cmpd	R	**cmpd**	R
3a	NH_2	**3c**	$CH_2CH_2NH_2$
3b	CH_2NH_2	**3d**	$CH_2CH_2N(CH_3)_2$
		3e	$NH(C{=}NH)NH_2$
Cmpd		R	
4a,**c**		1-adamantyl	
4b,**d**		(±)-10-camphorsulfonyl	

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DESIGN OF MULTIFACETED ANTIOXIDANTS: SHIFTING TOWARDS ANTIINFLAMMATORY AND ANTIHYPERLIPIDEMIC ACTIVITY

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The contribution of oxidative stress and inflammation in a multitude to pathological conditions is well established over the last decades. The correlation between various oxidative and inflammatory mechanisms and the development of multifactorial diseases such as atherosclerosis, diabetes, neurodegenerative and rheumatoid arthritis, has shifted research interest from a “one molecule-one target” to a “one molecule-multiple targets” approach. In these terms, the focus of this work is the design and study of pluripotent antioxidants which combine different properties including anti-inflammatory, free radical scavenging and antihyperlipidemic action. A series of 15 new derivatives by combining non-steroidal anti-inflammatory bioactive molecules with antioxidant functional moieties have been designed, synthesized and evaluated both *in vitro* and *in vivo*. This incorporation of multiple pharmacophores in the same structure led to an increase (2-10 fold) in both antioxidant and antiinflammatory profile, compared to reference bioactives/drugs, while some derivatives exhibited an interesting antihyperlipidemic activity. This work may compliment the latest trends in antioxidant drug development and may benefit our rational drug design strategy and practice.

IN SILICO STUDY OF LIPOXYGENASE INHIBITORS

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Introduction: Lipoxygenases (LOXs) are a group of enzymes involved in the biosynthesis of leucotrienes, the excess production of which is involved in inflammatory disorders. They catalyze the addition of molecular oxygen into polyunsaturated fatty acids (PUFAs) to give their respective hydroperoxy derivatives. Substrates (and respective inhibitors with therapeutic interest) interact with the large catalytic domain of the enzyme that contains a single atom of non-heme iron coordinated with three His residues. LOXs are ubiquitous among eukaryotic organisms (from mammals to plants) and show close functional and structural similarity between them.

Aim: The performed *in silico* study aims to investigate the pharmacophore features and binding mode of a set of 40 (in vitro evaluated) inhibitors of soybean LOX. The results of the study could be helpful in understanding: a) which are the key residues involved in the protein binding site and b) ligand pharmacophore features that play a major role in enzyme inhibition. Additionally, the investigation of structure-activity relationships for these ligands may indicate significant properties that improve potency and can thus be eventually used for the design of more efficient inhibitors.

Docking studies: In order to gain insight into the interactions between the studied compounds and the active site of soybean LOX, docking studies were performed using the Schrödinger Maestro suite.[1] The crystal structure selected for docking was PDB: 1IK3[2] and the protein was prepared with the default settings of the Protein Preparation Wizard. Ligands were prepared with LigPrep. Docking experiments were performed with Glide and Induced Fit Docking protocols.

QSAR study: In order to investigate properties of the compounds that mostly influence the inhibitory activity against LOX (*in vitro* inhibition studies), a set of 2D descriptors, using MolconZ software, was correlated with experimentally-determined activity. Additionally the docking poses of all inhibitors studied derived a SAR model revealing important interaction inside the binding pocket.

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2-OXOESTER PHOSPHOLIPASE A2 INHIBITORS WITH ENHANCED METABOLIC STABILITY

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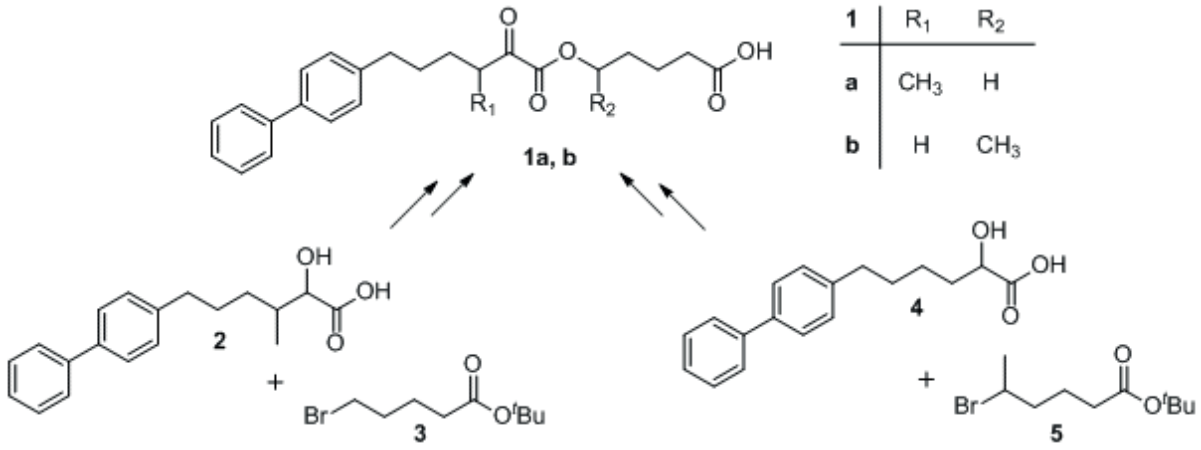
2-Oxoesters constitute a novel class of potent and selective inhibitors of human cytosolic phospholipase A_2 (GIVA $cPLA_2$), combining an aromatic scaffold or a long aliphatic chain with a short aliphatic chain with a free carboxylic acid [1]. In 2018, more potent 2-oxoester inhibitors of GIVA $cPLA_2$ have been reported, but their rapid degradation in human plasma limits their pharmaceutical utility [2]. For this reason, the need for enhanced metabolic stability of these compounds has emerged and this has been achieved by the introduction of a methyl group either on the α-carbon atom to the oxoester functionality or on the carbon carrying the ester oxygen. The methyl group is the smallest alkyl group and has played a protagonistic role in drug design by being the problem-solving key to their lead optimization [3]. Mainly, the PharmacoKinetic (PK) and PharmacoDynamic (PD) properties of the molecule can be modified by the addition of the methyl group, where in many cases an increase in the selectivity and potency of the medical agent is noticed [3]. In our case, the target compounds are 2-oxoesters consisting of a 2-oxo-hexanoic acid scaffold bearing a biphenyl on the left and a valeric acid scaffold on the right, with a methyl group either on the left or the right of the oxoester functionality (**1a**, **b**) each time. The synthesis began when 4-biphenyl carboxaldehyde has undergone a Horner-Emmons reaction and after a hydrogenation has afforded the corresponding saturated fatty acid. At this point, with LDA, HMPA and CH_3I treatment α-methyl fatty acid was obtained, which after appropriate transformations gave the β-methyl-α-hydroxy carboxylic acid **2**, which reacted with bromo tert-butyl-pentanoate **3**. Dess Martin oxidation and deprotection of the tert-butyl ester by 50% TFA sol. afforded **1a**. Following a similar synthetic strategy, α-hydroxy acid **4** reacted with tert-butyl-5-bromohexanoate **5**. 5-Bromohexanoic acid was obtained by a delta-hexalactone ring opening with 33% HBr in AcOH reaction. Dess Martin oxidation and reaction with 50% TFA sol. afforded **1b**. The stability of **1a** and **1b** in human plasma was studied in a time-dependant manner employing a liquid chromatography-high resolution mass spectrometry (LC-HRMS) method. A significant increase in the metabolic stability, in comparison with the non-substituted inhibitor GK452 [1], was observed in both cases.



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DESIGN SYNTHESIS AND EVALUATION OF NOVEL ALDOSE REDUCTASE INHIBITORS: THE CASE OF INDOLYL-SULFONYL-PHENOLS

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Therapeutic interventions with aldose reductase inhibition appears to be a promising resolve for major pathological conditions (i.e. neuropathy/angiopathy related to chronic hyperglycemia, chronic inflammation and cancer). As of now, the most potent aldose reductase inhibitors are carboxylic acid derivatives, which poorly permeate biological membranes. In this work, continuing our previous works, we emphasize in the bioisosteric replacement of the carboxylic acid moiety to make equally potent and more drugable inhibitors.

ANTICANCER ACTIVITY OF O-ALKYL DERIVATIVES OF NARINGENIN AND THEIR OXIMES AGAINST HUMAN COLON CANCER CELL LINE HT-29

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Naringenin (4',5,7-trihydroxyflavanone) belongs to a large group of polyphenolic compounds known as flavonoids. It occurs in citrus fruits such as grapefruits or oranges and is responsible for bitter taste [1]. Naringenin as well as its *O*-alkyl derivatives – sakuranetin (7-*O*-methylnaringenin) and 7-*O*-butylnaringenin exhibited a variety of biological activities such as antioxidant, anticancer, anti-inflammatory, antibacterial and antifungal [2-4].

The aim of our investigation was to synthesize a library of *O*-alkyl derivatives of naringenin bearing methyl, ethyl, propyl, isopropyl, butyl, pentyl, decyl and dodecyl groups attached to hydroxyl moieties at the C-4', C-5 and C-7 positions with yields up to 79%. In the next step, all *O*-alkyl derivatives of naringenin were used as a substrates in reaction with hydroxylamine hydrochloride in which 19 oximes were obtained. Structures of all products were confirmed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and high resolution mass spectrometry (HRMS).

Anticancer activity of *O*-alkyl derivatives of naringenin and their oximes was tested on human colon cancer cell line H-29. The cytotoxicity was calculated as IC_{50} value and compared to reference compounds – doxorubicin and cisplatin. The strongest antiproliferative activity was observed for 7,4'-di-*O*-butylnaringenin oxime and 7-*O*-decylnaringenin oxime with IC_{50} value of 3.32±0.29 $\mu g \cdot mL^{-1}$ and 3.63±0.47 $\mu g \cdot mL^{-1}$, respectively. Then, the studies were planned to determine the mechanism of action of the compounds. Preliminary results, based on Annexin V/PI dual staining, analysis of caspase 3 and PARP level by immunoblotting and the determination of genomic DNA fragmentation, excluded the possibility of compounds acting by the apoptosis activation.

This work was supported by the National Science Centre, Grant no. 2016/21/B/NZ9/01904.

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TO MOLECULAR DIVERSITY VIA AMINOVINYLKETONES AND THEIR TRANSFORMATIONS PRODUCTS: ACYL(IMIDOYL)KETENE FTIR-SPECTROSCOPY REGISTRATION AND SELECTED CHEMOTYPES BIOLOGICAL ACTIVITY ASSESSMENT

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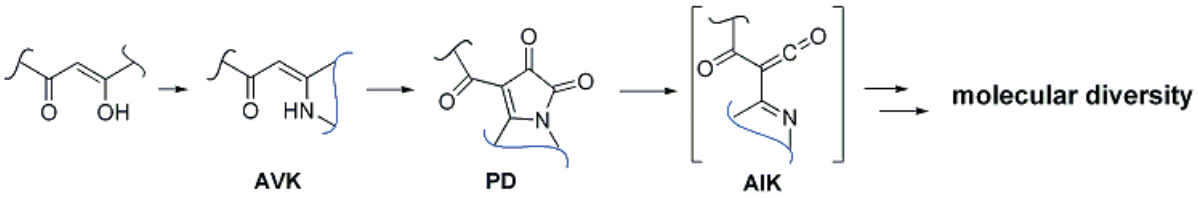
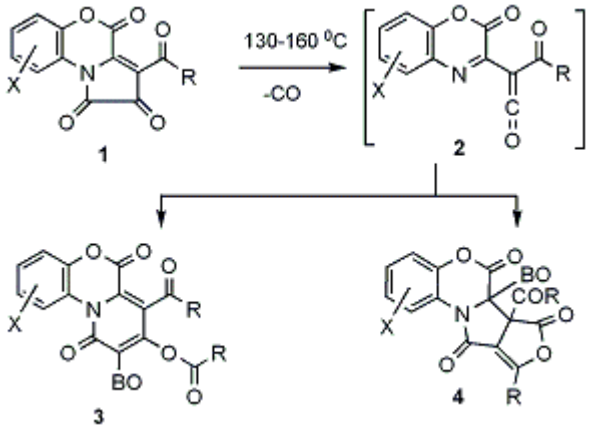
One of the examples 3-amino-2-propenones (aminovinylketones, AVK) chemistry successful utilization is based on their diacylation leading to 4-acylpyrrole-2,3-diones (PD). The latter represent a long known[1,2] advantageous chemotype allowing an access to diverse range of heterocyclic systems via various transformations actively studied in recent years. Thermal decarbonylation leading to reactive and multifunctional acyl(imidoyl)ketenes (AIK) is one of the productive directions serving further molecular diversity attaining.



Substituents at both acyl and imidoyl moieties in AIK may greatly influence reactivity and, therefore, stability of generated intermediates. Acyl(imidoyl)ketenes formed from [a]-annulated PDs are quite stable which has allowed - at the first time - direct registering their presence in the reaction mixture. It was done for pyrrolo[2,1-c][1,4]benzoxazintriones (**1**) decarbonylation reactions at comparatively mild conditions of 125–150°C *in situ* with application of FTIR spectroscopy. The ketene bond in **2** appeared at 2110-2120 cm^{-1}. Known dimerization via [4+2] cycloaddition reaction[3] and a new type of dimerization via formal [4+4] cycloaddition were observed. Dimerization products of both types undergo further rearrangements leading to the stable final products **3** and **4** correspondingly.



"Drug-likeness" related properties and some biological activity data for the representative examples of chemotypes in the sequence from AVK toward the end products will be reported.

The study was partially funded by Government of the Perm Region within the research project No.C-26/174.2

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SYNTHESIS OF NOVEL 1,2,4-TRIAZOLE DERIVATIVES WITH TUBERCULOSTATIC ACTIVITY

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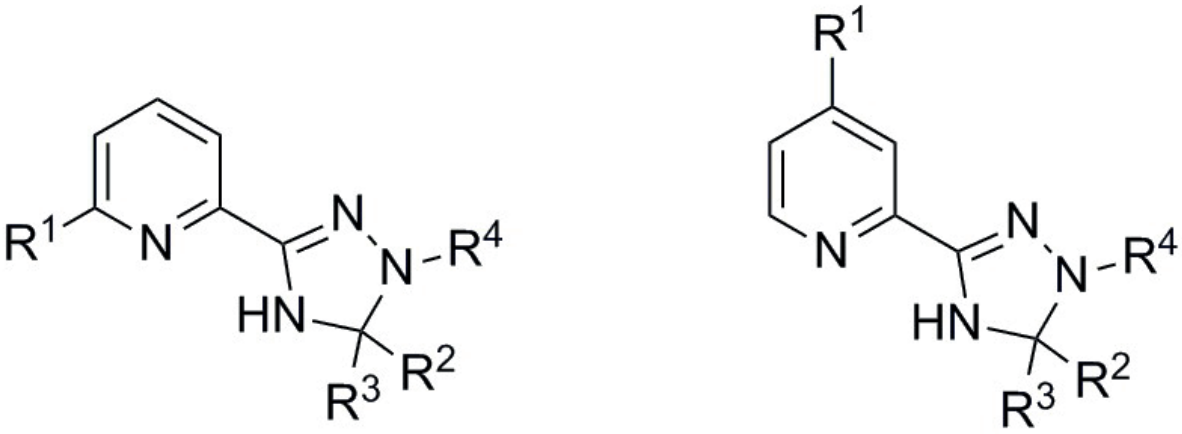
For the last several decades the world has observed an increase in the number of infections caused by resistant strains of pathogenic microorganisms. This phenomenon applies also to tuberculosis resistance which is a special case of an infectious disease. While the total number of infections caused by *Mycobacterium tuberculosis* appeared to be unchanged in the continent, the number of infections caused by multi-drug resistant strains or multi-drug-resistant tuberculosis (MDR-TB) case has been found to have increased. The chemotherapeutic therapy of multidrug-resistant tuberculosis is difficult. The most effective drugs such as isoniazid or rifampicin are no longer effective[1].

Triazole derivatives have a variety of biological activities, including antibacterial and antitubercular activity[2]. The aim of our study was design, synthesis and evaluation of biological activity of novel 1,2,4-triazole derivatives of 6- and 4-chloropicolinonitrile derivatives. The first step of the synthesis was the nucleophilic substitution of chlorine atom of picolinonitrile by morpholine, pyrrolidine, phenol or thiophenol. Subsequently 4-substituted picolinonitriles were conducted into 4-substituted picolinimidates in the presence of methanol and catalytic amounts of DBU. Amidrazone derivatives were obtained by reaction of iminoesters with hydrazine and then they were cyclized in the presence of triethyl orthoformate or heterocyclic methyl ketones. All compounds were characterized by IR, ^{1}H NMR spectra and elemental analysis.



They have been tested for tuberculostatic activity in vitro against M. tuberculosis strains: H_{37}Rv and Spec. 210. The obtained compounds showed a variety of tuberculostatic activities.

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APPLICATION OF A NOVEL BIO-POLYMER CYCLIC BETA GLUCANS AS NANO-CARRIER FOR DRUG INCLUSION COMPLEX FORMATION

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Cyclic beta glucans (CBGs) are biopolymer consisting of glucose units having α- and β- linkages forming a cyclic structure . They are cell surface polysaccharides mainly located in the periplasmic region of the bacteria from Rhizobiaceae family. They are known to be biocompatible and antitumorogenic molecules with immunostimulating activity. They have unique structure with a larger hydrophobic inner cavity and a hydrophilic surface which facilitates them as nanocarrier for inclusion complex formation with a wide variety of guests. The use of CBGs for encapsulating tuberculosis (TB) drugs can protect the guest from environmental conditions and improve the aqueous solubility and hence it's bio-availability.
Here, the drug-CBG inclusion complex was prepared using coprecipitation method followed by freeze-drying method. Three commonly used drugs for TB treatment namely, Rifampicin, isoniazid, and pyrazinamide were employed for the current study. The confirmation of the formation of the inclusion complex was performed with UV-Vis spectrophotometer, FTIR and SEM. The encapsulation efficiency and antibacterial activity of the inclusion complex was also studied. UV-Visible spectrum (Fig.1 (A)) and FTIR spectroscopy (Fig.1(B)) showed that interaction of rif with CBG led to a shift in the major characteristic peak of it, from 473 to 574 nm. The solubility of the drug is increased in the complex by 71%.The initial results confirmed the formation of nanoparticle-drug inclusion complex. Moreover, SEM results confirms the formation of inclusion complex. The comparative study for the effect of inclusion complex formation on the antibacterial study is also performed.

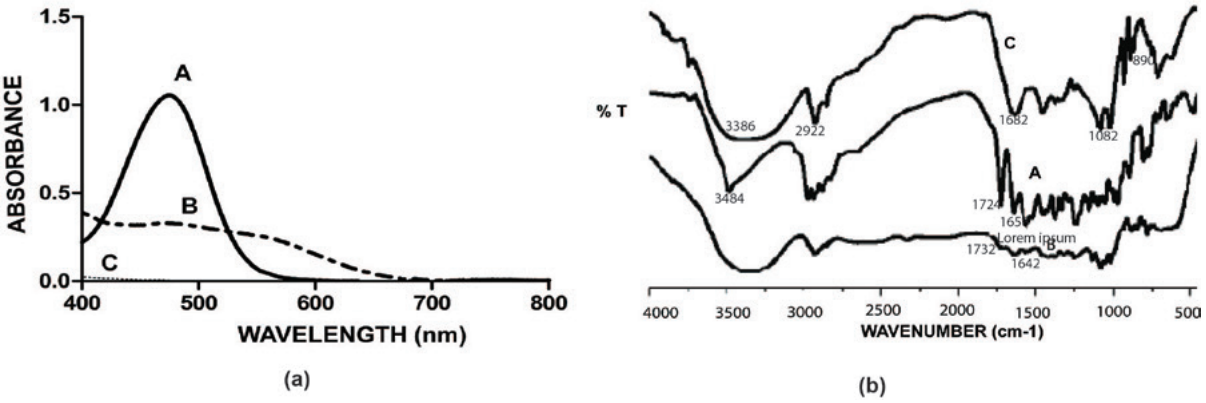

Fig.1(A) UV-Visible spectrum & (B)FTIR of CBG-drug complex for CBG-drug complex. a: Rifampicin, b: CBG-rifampicin Complex and c: CBG

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MACROCYCLIC PEPTIDOMIMETICS: LIBRARY DESIGN AND SYNTHESIS

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Remarkably growing interest toward medium- and large-sized heterocycles is not accidental since it is closely linked with the growing interest toward protein-protein interactions (PPI) as promising therapeutic targets and therefore small molecule PPI modulators. On the other side, set of synthetic tools capable of producing large libraries of macrocyclic compounds is rather limited.

We have used two methodologies for the design and synthesis of macrocyclic peptidomimetics library. One of them includes ring expansion employing Bormann-Wasserman strategy (BWS) and allows synthesizing 10-12-membered lactams. This gives us access to unique functionally enriched, spiro- and fused scaffolds with incorporated (un)substituted b-alanine moiety. The other one is based on click-macrocyclization of linear peptidomimetics bearing acetylene and azide functionalities at the ends to provide 14-22-membered macrocyclic peptidomimetics. Both methodologies have been applied for the synthesis of macrocyclic scaffolds with additional functionalities applicable for further diversification. This allowed us to synthesize successfully multi-thousand-member library of macrocyclic peptidomimetics.

LIBRARY OF COVALENT INHIBITORS: DESIGN AND SYNTHESIS

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Historically, covalent drugs have made a major impact on human health. The list includes many important therapeutics such as aspirin, penicillin, cephalosporin, fosfomycin, omeprazole, clopidogrel, and others. However, during the last decade of the 20-th century the drug discovery research has been revolving around Lipinski's rules while systematically discarding covalent inhibitors. Nevertheless, a covalent mechanism of action has numerous pharmacological advantages including enhanced potency, selectivity, and prolonged duration of action.[1]

For the last decade or so, there was a steadily growing interest in covalent binders. The number of citations of covalent inhibitors in the scientific literature have almost quintupled since 2009.[2] Furthermore, covalent binders are becoming increasingly important in fragment-based drug discovery. Following this trend, we have synthesized the rationally designed diverse library of covalent inhibitors.

The library was designed for covering the most frequent warheads currently used as covalent reactive groups (CRG) such as chloroacetyl, 2-chloropropanoyl, acryloyl, 1-prop-2-ynoyl, 1-but-2-ynoyl, and others. A diverse set of unique and/or rare amines (non-covalent units, NCU) has been picked from our collection of the stock-available building blocks. Criteria for NCU selection in the library design will be presented.

Over 2000 covalent binders have been synthesized so far, and the number of library members continues to grow. Importantly, over 900 library members meet fragment criteria for their NCUs.

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NANOCYCLIX: NEXT GENERATION OF KINASE THERAPEUTICS A CHEMOCENTRIC APPROACH FOR THE DISCOVERY OF SELECTIVE KINASE INHIBITORS

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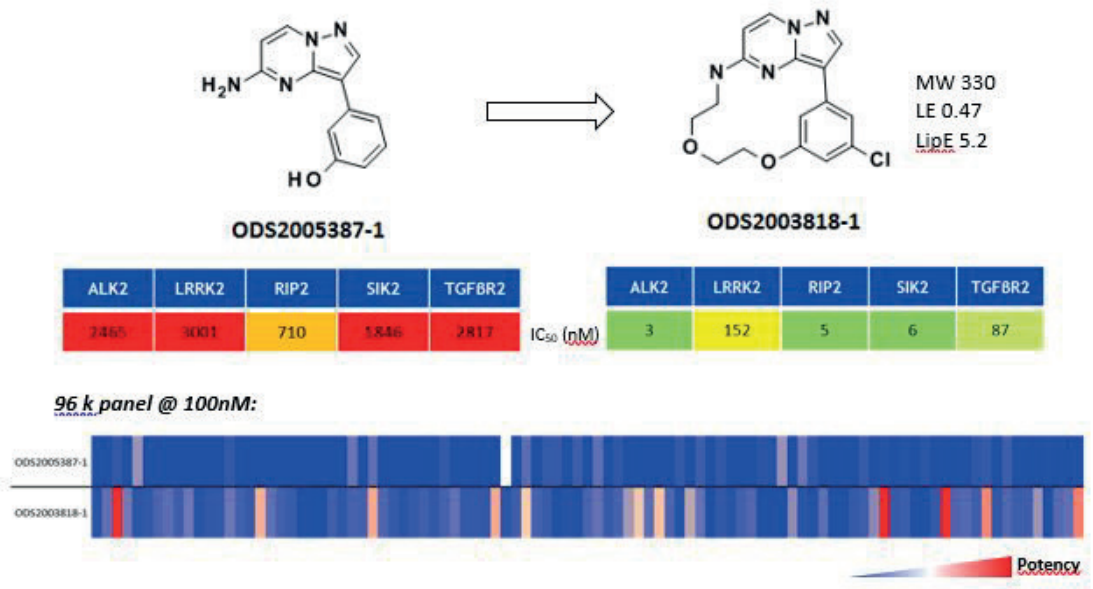
Nanocyclix is a kinase focused library of small macrocyclic hinge binder molecules. This library was designed using a chemocentric approach to identify attractive and selective kinases inhibitors. All the compounds are in the drug-like properties space and hit compounds display nanomolar potencies and good selectivity against a small number of kinases. Nanocyclix design is based on the macrocyclisation paradigm of known hinge binder scaffolds resulting in tighter binding site recognition, potency and selectivity towards the ATP site. Exploring different lengths and functionalities of the cyclic linker allow populating the conformational space of every template and to identify an optimal match between the size and mobility of the binding site and the macrocyclic ligand. Potent and selective inhibitors of therapeutic kinases such as LRRK2, RIPK2 and ALK1 have been identified by this approach and their optimization to advanced lead will be briefly described.



"Signature" of first generation compound ODS2003818 (386 kinases panel) shows high potency with selectivity for small subset of kinases

HYDROXYTYROSOL (HT) ANALOGS AS POTENT ANTIFUNGALS. IN VIVO AND IN-SILICO STUDIES FOR DIRECT DISRUPTION OF THE FUNGAL CELL MEMBRANE

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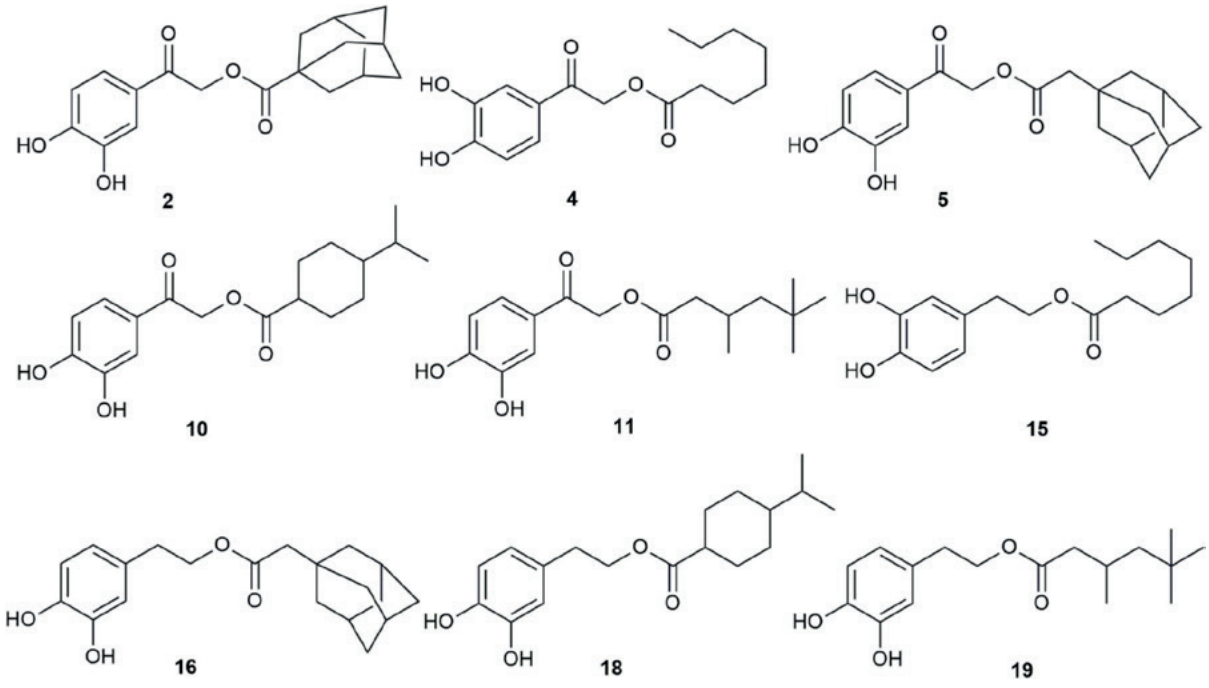
Fungal infections comprise an emerging threat due to increasing number of immunocompromised people and pharmacological or other treatments aiming at viral infections, cancer or allergies. Over the last 20 years no new classes of antifungals have been approved, emphasizing the urgent need for developing a novel generation of antifungals. We synthesized and in-vivo evaluated the antifungal activity of a series of chemically synthesized Hydroxytyrosol (HT) analogs. HT is one of the major phenolic compounds in olive oil, shown to possess radical-scavenging antioxidant, antiproliferative, proapoptotic and anti-inflammatory activities. No previous report has studied HT analogs as antifungals. We show that specific analogs have broad and strong antifungal activity, significantly stronger than the parent compound HT. Using *Aspergillus nidulans* as an *in vivo* cellular model system, we show that antifungal HT analogs have an unprecedented efficiency in fungal plasma membrane destruction. Importantly, antifungal HT analogs did not show toxicity in a mammalian cell line, whereas no resistance to HT analogs was obtained by standard mutagenesis. Finally, we utilized Umbrella Sampling method to calculate the Free Energy of Translocation for the most potent analogs and validate the disruption of the fungal cell membrane.



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SYNTHESIS AND BIOLOGICAL EVALUATION OF DEHYDROEPIANDROSTERONE 17-SPIRO-CYCLOPROPYL DERIVATIVES WITH NEUROTROPHIC AND NEUROPROTECTIVE ACTIVITY

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Neurosteroids affect survival, development and function of neurons and it has been found that their levels in the brain reduce with aging and in neurodegenerative diseases. Recent studies have shown that the neurosteroid dehydroepiandrosterone (DHEA) acts as neurotrophic factor in the brain and prevents neuronal apoptosis by interacting with the neurotrophin receptors TrkA and $p75^{NTR}$.[1] Neurotrophins are a family of growth factors that regulate proliferation, differentiation and survival of neural cells. This family consists of four growth factors, namely nerve growth factor (NGF), brain-derived growth factor (BDNF), neurotrophin-3 (NT3) and neurotrophin-4/5 (NT-4/5). Each neurotrophin binds to its respective high affinity Trk receptor (NGF to TrkA, BDNF and NT3 to TrkB, and NT4/5 to TrkC) and all neurotrophins withlow affinity to $p75^{NTR}$ receptor. A number of studies corroborated that neurodegeneration is due, at least in part, to changes in expression of neurotrophins and/or their receptors. Nevertheless, DHEA is metabolized in humans into estrogens and androgens, thus its long-term administration is increasing the risk for hormone-dependent cancer. Therefore, DHEA analogues with modifications at position C17 of the steroid skeleton were synthesized aiming to improve the neuroprotective and antiapoptotic activity of the parent molecule, without the undesired hormonal side effects.[2,3,4]

In the current work the synthesis of chiral 17-spirocyclopropyl DHEA derivatives will be described. A variety of pharmacophore groups as substituents of the cyclopropyl moiety were introduced, in order to obtain Structure-Activity-Relationships for neurotrophin mimetic activity. The new compounds were evaluated for their agonistic activity on neurotrophin receptors TrkA, TrkB and $p75^{NTR}$ on NIH-3T3 -stable transfected with each receptor- cells, while their anti-apoptotic activity was evaluated using the neural crest-derived PC12 cell line. Moreover, we tested their effect on inflammatory responses of LPS-stimulated microglial cells.[5] Furthermore, preliminary *in silico* screening studies were performed to examine the possible binding sites of the new compounds on neurotrophin receptors.

Acknowledgement

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6-SUBSTITUTED NAPHTHO[2,1-B]BENZOFURANS AS NOVEL DUAL-STATE EMISSIVE FLUOROPHORES WITH BLUE EMISSION

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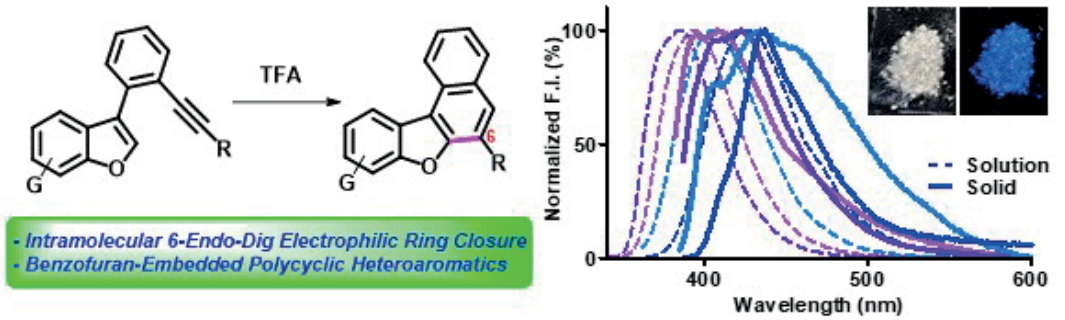
In this work, we have developed a modular approach to a wide range of 6-substituted naphtho[2,1-*b*]benzofurans by way of sequential Sonogashira cross-coupling and intramolecular 6-endo-dig electrophilic cyclization. Screening of the synthesized compounds using a high-content imaging system enabled us to discover novel dual state emissive compounds **2**{*1,6*}, **2**{*1,8*}, and **2**{*4,3*}, which are highly emissive with blue emission in their solid states as well as in solution states in most solvents. In addition, the compounds **2**{*4,3*}, **2**{*4,12*}, and **2**{*5,13*} were found to be the most cell permeable in HeLa cells for live cell imaging with negligible phototoxicity. The compounds we developed in this work would serve as a novel fluorescent scaffold with a variety of biomedical and optoelectronic applications.



DIASTEREOSELECTIVE SYNTHESIS OF 1,3-AMINOALCOHOLS USING AU-CATAYLZED CYCLIZATION AND RING OPENING METHOD

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1,3-Amino alcohols are an important structural motif of organic compounds that not only are widely found in natural products and pharmaceuticals but also are useful synthons for organic transformations. They are frequently observed in commercial pharmaceuticals or in bioactive natural products. Lopinavir (**1**, Figure 1), a FDA-approved anti-HIV drug and fluoxetine (**2**, Figure 1), the antidepressant drug well-known as Prozac have 1,3-aminoalcohol moiety. Tubulysin D (**3**, Figure 1), the most potent antimitotic agent also has this moiety. Although the stereochemistry of 1,3-aminoalcohol is very important for the bioactivity and the potency of the pharmaceuticals, only a few examples for stereoselective synthesis of 1,3-aminoalcohols are known. In this study, we report a synthetic protocol of various cyclic precursors of 1,3-aminoalcohols via an Au-catalyzed intramolecular cyclization. 5 mol% of Au catalysts facilitated the reactions at room temperature and afforded cyclic precursors of 1,3-aminoalcohols in moderate to good yields (yield up to 68.2%) and good diastereoselectivity (dr up to 6.69:1). The ring-opening reaction of cyclic precursors led to the 1,3-aminoalcohols in good yields.

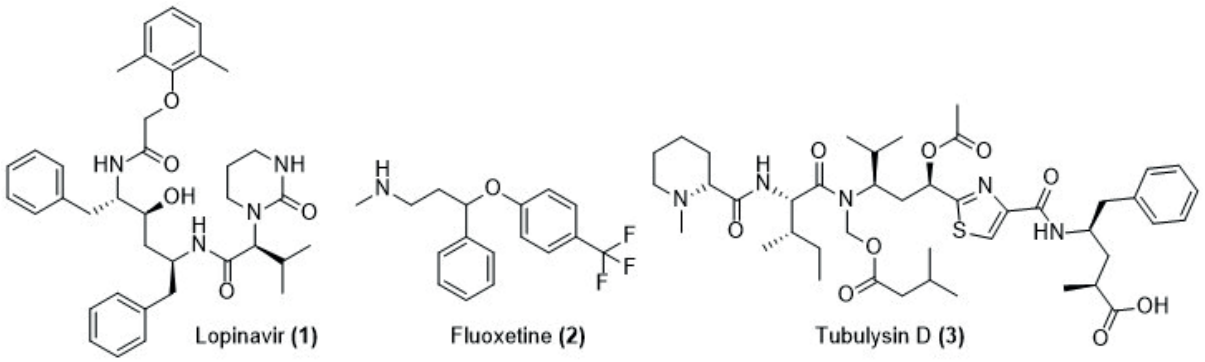

Figure 1. Lopinavir (**1**), Fluoxetine (**2**) and Tubulysin D (3)

DEVELOPMENT OF A NOVEL TURN-ON FLUORESCENT BIOSENSOR FOR SELECTIVE DETECTION OF CELLULAR Fe3+ IN LYSOSOMES

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Iron-selective turn-on sensors are indispensable tools for understanding iron-related cell death processes and human diseases. In this study, we report a novel class of fluorescent sensors derived from an indolizino[3,2-c]quinoline scaffold that exhibit high selectivity for Fe3+ over other biologically abundant cations in cells, including Fe2+, Al3+, Zn2+, and Mn2+. IQ18 works as a ratiometric sensor with a Kd value of 7.1×10 −7M and a detection limit of 5.2 nM in ethanol, whereas IQ44 displays fluorescence enhancement upon binding with Fe3+ in both ethanol and water. In aqueous solution, IQ44 exists as 150-nm nanoparticles. The suppressed fluorescent emission of IQ44 nanoparticles in water is switched on in response to Fe3+, working as a turn-on nanoparticle sensor. Structure-property relationship analysis with IQ derivatives revealed that the thiophene ring confers selectivity for Fe3+. By installing thiophene in IQ44 as a selectivity-tuning handle, fluorescence in the presence of Fe3+ resulting from restriction of intramolecular rotation (RIR) and increased torsion angle induced by iron demonstrated that IQ44 is specifically localized in lysosomes, where it recognizes cellular Fe3+ in live cells, as determined using confocal microscopy. In addition, the increased fluorescent puncta of IQ44 in the presence of Fe3+ colocalized well with the RFP-tagged LC3 proteins (pmRFP-LC3), enabling the detection of the autophagy process.

ACTIVITY-BASED-PROBING OF RHODESAIN: A VINYL SULFONE DERIVED INHIBITOR WITH A BIMODAL FLUORESCENCE LABEL

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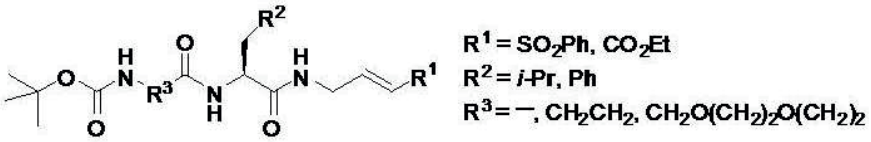
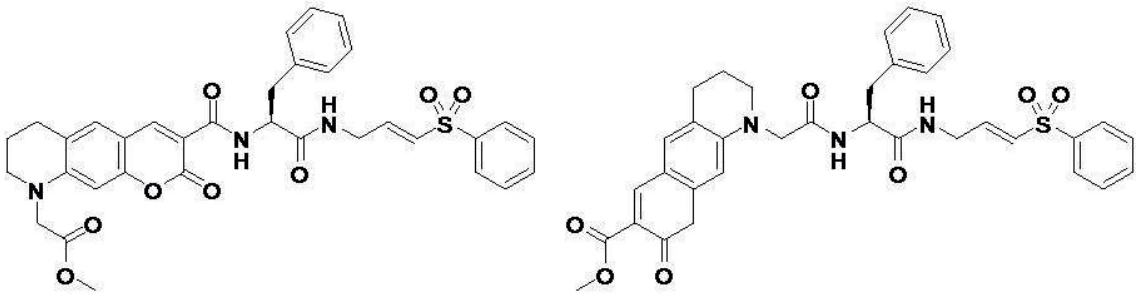
Cysteine proteases play an important role for the pathogenesis of several parasites causing infectious tropical diseases. Rhodesain is a cathepsin L-like cysteine protease and is the major cysteine protease of Trypanosoma brucei rhodesiense, the parasite which is responsible for African trypanosomiasis, a type of sleeping sickness. Targeting these proteases by Michael acceptors is a widely common method for inhibition of the parasite's life cycle.[1]



Herein, a series of inhibitors has been designed and synthesized following a combinatorial approach. The compounds bear an α,β-unsaturated phenyl vinyl sulfone or ethyl acrylate warhead and a peptidomimetic portion aligned to the non-primed binding region.[2] Biochemical evaluation towards the four human cathepsins B, K, L and S as well as rhodesain was carried out and the kinetic characterization confirmed an irreversible mode of inhibition. Interestingly, the most potent inhibitor against rhodesain with an inactivation constant of 114,000 M^{-1} s^{-1} was only weakly active at human cathepsins, thus providing an excellent starting point for a selective activity-based probe (ABP).



An activity-based probe for rhodesain was thus prepared and kinetically characterized. The compound bears a new type of bimodal coumarin that can be implemented on different ways. Synthesis of these coumarins was established in moderate yield following a seven-step-approach. While a methyl ester at each coumarin was maintained, a tert-butyl ester was cleaved prior to the final coupling step. The resulting ABP candidates were investigated to elucidate the suitability for enzyme inactivation and labelling by means of SDS-PAGE and Fluorescence-HPLC.[3] The incorporated bimodal coumarin leaves space for further derivatization at the corresponding protected ester group.

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PEPTIDIC α-KETOAMIDES AS AN INHIBITORS OF PfSUB1

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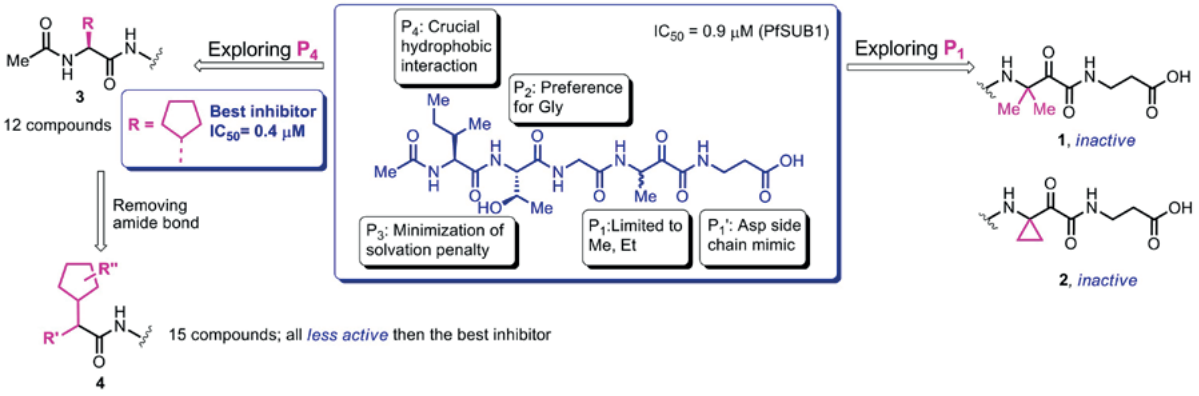
Malarial serine protease (PfSUB1) is known to be involved in parasite invasion and egress from human red blood cells and therefore PfSUB1 has a potential to be exploited as anti-malarial drug target [1]. Previously we have developed peptidic PfSUB1 inhibitors containing α-ketoamide warhead [2]. Initial SAR investigations revealed the crucial interactions of peptidic part of ketoamide inhibitors.



Here we report the studies aimed to explore the optimal substituents for sub-pockets P_1 and P_4. Di-substitution at P_1 position gave inactive compounds 1 and 2. However, variation of P_4 position (compounds 3) revealed that c-Pent group as the most optimal substituent leading to improved inhibitory potency. Further attempts were made to replace acetamido groups, however none of inhibitors 4 showed better activity compared to parent compound 3.

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DISCOVERY OF FIRST IN VIVO ACTIVE INHIBITOR OF THE PHOSPHATASE ACTIVITY OF SOLUBLE EPOXIDE HYDROLASE

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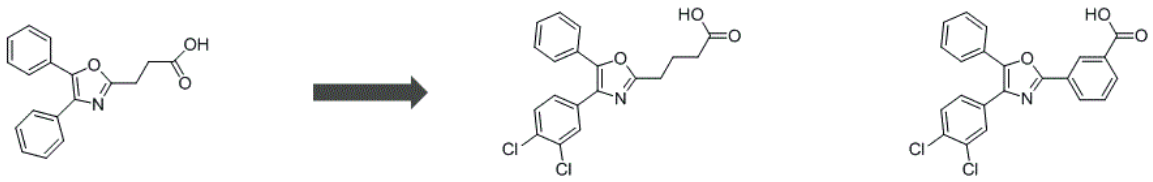
The emerging pharmacological target soluble epoxide hydrolase (sEH) is a bifunctional enzyme exhibiting two different catalytic activities, which are located in two distinct domains.[1] Although the physiological role of the hydrolase domain is well-investigated[2], little is known about the phosphatase activity, located in the N-terminal domain of the sEH (sEH-P).[3] One of the main reasons for this is the lack of high-affinity inhibitors, which can be used as chemical probes[4] to investigate its physiological role.



Oxaprozin SWE101 SWE102

Herein we present the first affine inhibitors for the human and rat sEH- phosphatase domain. Starting from an HTS hit Oxaprozin we expanded the SAR using a fluorescence-based activity assay[5]. The most potent inhibitor SWE101 was then further characterized by ITC and differential scanning fluorimetry (DSF). SWE101 is a potent sEH-P inhibitor with a favourable selectivity profile. X-ray analysis of the sEH phosphatase domain complexed with an inhibitor provides insights in the molecular basis of small-molecule sEH-P inhibition. SWE101 has an excellent pharmacokinetic and pharmacodynamic profile in rats and enables the investigation of the physiological and pathophysiological role of sEH-P in vivo.

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RATIONAL DESIGN AND SYNTHESIS OF 1,3,4-OXADIAZIN-5(6H)-ONES-BASED PHOTOAFFINITY LABELLING PROBES: TARGET IDENTIFICATION FOR ANTICANCER ACTIVITY

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Rational design and synthetic feasibility are critical factors for the photoaffinity labelling (PAL) approach, which can identify protein targets of bioactive small molecules under native cellular conditions. In this study, we developed 1,3,4-oxadiazin-5(6*H*)-ones-derived photoaffinity labelling probes (**OPALs**) for LL-2003, a previously reported potential anticancer agent against IGF-1R and Src. Our photoaffinity labelling strategy enabled successful photo crosslinking of the probes (**OPAL-6** and **OPAL-8**) with the target proteins in both mammalian cell lysates and live MCF7, A549, HepG2 and HeLa cells *in situ*. *In vitro* and *in situ* labelling demonstrated different patterns and expression levels of the proteome, and the strongest band for Src appeared in the A549 cell line. An in-gel fluorescence scan combined with MS/MS analysis of the IGF-1R overexpressed insect proteome labelled by **OPAL-6** and **OPAL-8** identified the binding location of the synthesized probes.

SYNTHESIS AND SAR OF 5-ARYL-FURAN-2-CARBOXAMIDE DERIVATIVES AS POTENT UROTENSIN-II RECEPTOR ANTAGONISTS

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Heart failure, in which abnormalities exist in both heart contraction and relaxation, has become a global pandemic. Incidences of this disease are continuously growing owing to the increase in the average age of the world population and the number of cardiovascular risk factors. Among many others, the urotensin-II (U-II) and urotensin-II receptor (UT) system has received great attention as a therapeutic target for treatment of heart failure because of the pivotal role it plays in the regulation of cardiovascular functions.U-II, composed of a cyclic neuropeptide bridged by cysteine, is also known to be one of the most potent vasoconstrictor. This peptide is expressed in a variety of tissues, including blood vessels, heart, liver and kidney. The effects of U-II are regulated by its binding to UT,upon which it exerts complex signal transduction that induces a variety of physiologically cardiovascular responses including vasoconstriction, vasodilation, cell proliferation and hypertrophy. In addition, observations made in a number of previous basic pharmacological and clinical studies demonstrate that expression of UT is low or undetectable in normal myocardium. In contrast, both the concentration of U-II plasma and amount of tissue expression on UT are greatly increased in numerous cardiorenal and metabolic diseases, including hypertension, heart failure, atherosclerosis, diabetes and renal failure. Additional investigations have demonstrated that several UT antagonists improve cardiac hypertrophy and cardiac dysfunction in various animal models.Therefore, antagonism of UT is considered to be one of the most promising therapeutic strategies for treatment of heart failure as well as a wide range of other cardiovascular diseases.In the search for effective UT receptor antagonists, we recently identified a series of 5-arylfuran-2-carboxamide derivatives, bearing a 4-(3-chloro-4-(piperidin-4-yloxy)benzyl)piperazin-1-yl group. The results of a systematic SAR investigation of furan-2-carboxamides with C-5 aryl groups possessing a variety of aryl ring substituents led to identification of the 3,4-difluorophenyl analog as a highly potent UT antagonist with an IC_{50} value of 6 nM. In addition, this substance was found to display high metabolic stability, and low hERG inhibition and cytotoxicity, and to have an acceptable PK profile.

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EVOLUTION OF THE SYNTHETIC ROUTES TOWARDS AZD4573, A POTENT AND SELECTIVE INHIBITOR OF CDK9

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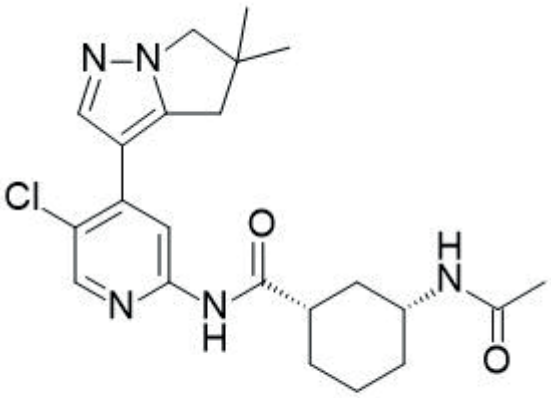
AZD4573 is a highly potent and selective CDK9 inhibitor with favourable physical properties and preclinical pharmacokinetics (short half-life) for high but transient CDK9 inhibition after intravenous administration, allowing high flexibility in the dosing schedule in order to optimize the efficacy / tolerability balance in the clinic. In vivo, AZD4573 induced tumour regression in preclinical haematological tumour models after episodic dosing and is currently in Phase 1 clinical trials for haematological cancers.

We will report selected SAR in the optimization of this series with a focus on pharmacokinetic and physicochemical properties, leading to the identification of AZD4573, and the routes used to prepare these compounds. Our medicinal chemistry synthetic routes will demonstrate a flexible modular approach to analogues with emphasis on the variation of the headgroup and core changes.

We will also report the evolution of the synthetic route to AZD4573 from initial synthesis to the campaign 1 route (c.a. 50 g of drug substance in high yield and chiral purity). The convergence of the route allowed maximum flexibility and allowed candidate selection to be taken late in the process. Highlights of the route include a high yielding cyclisation, Wolff-Kishner reduction and borylation sequence towards a complex pyrazole boronic ester and an enzymatic resolution to provide the key cyclohexylamino acid amide with >99.9% ee. Combined, these features provide a highly efficient process for the preparation of initial batches of drug substance.



AZD4573

ENCAPSULATION OF 4-MU IN FUNCTIONALIZED PLGA NANOPARTICLES FOR TARGETING LIVER CANCER

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Hepatocellular Carcinoma (HCC) is the most frequent primary liver cancer in adults, and represents the third cause of cancer-related death worldwide. It occurs in the setting of chronic liver disease or cirrhosis due to chronic hepatitis B and C viral infection, alcohol abuse, and nonalcoholic fatty liver disease.[1] The liver injury is characterized by an excessive accumulation of extracellular matrix components including hyaluronic acid (HA). An abnormal production of HA is also closely linked to a cancerous condition, because stromal HA may create a permissive extracellular microenvironment for tumor progression and metastasis through cancer cell proliferation, migration, and invasion. Thus, HA signaling is expected to be a target for anticancer therapy.[2]

4-Methylumbelliferone (4-MU) is a synthetic coumarin derivative (7-hydroxy-4-methylcoumarin), and it is an effective inhibitor of HA synthesis with potential therapeutic benefits for treating cancer.[3] In spite its positive effects against different diseases, 4-MU manifests a very poor bioavailability in vivo, due to its low aqueous solubility and minimal absorption in gastrointestinal tract, that definitely limits its use in biomedical applications.

The objective of this work is to propose a drug delivery system based on poly(lactic-co-glycolic acid) nanoparticles (PLGA-NPs) loaded with 4-MU, for the treatment of HCC. PLGA-NPs with hydrodynamic diameter of <150 nm are synthesized by nanoprecipitation technique, and completely characterized. The novelty of the proposed system is the NPs surface functionalization with hyaluronic acid binding proteins (HABP), that function as targeting moieties toward tumor liver cells while limiting the opsonisation of PLGA-NPs. Finally, the anticancer effect of the system will be tested in order to demonstrate a potential therapeutic effect of such formulation.

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SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY EVALUATION OF NOVEL MULTISUBSTITUTED PYRAZOLO[3,4-b]PYRIDINES

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Although remarkable progress on the identification of novel anticancer targets has been achieved over the last two decades, cancer is still the second cause of death globally. Thus, the search for new derivatives that inhibit uncontrolled cell proliferation remains an active area of research, due to the continuous need for the development of novel chemotherapeutic agents. Among the anticancer agents currently being in clinical trials or in clinical use, purine isosters are of great significance, since a number of new drugs possess such an isosteric scaffold, mainly acting as kinase inhibitors, which mimick ATP in its binding pocket.[1]

As part of an on-going project concerning the synthesis of purine isosters with potential antiproliferative and kinase inhibitory activity, we have identified a great number of substituted pyrazolo[3,4-*c*]pyridines[2,3] and pyrrolo[3,2-*d*]pyrimidines,[4] possessing IC_{50} values in the low μm range against a panel of cancer cell lines. Herein, we describe the synthesis and the cytotoxic activity evaluation of some novel pyrazolo[3,4-*b*]pyridines, which bear suitable substituents at positions 1, 4 and 6 of this scaffold.

The synthesis of the novel derivatives was achieved upon ring-closure reaction of suitably substituted 5-aminopyrazoles, followed by insertion of the appropriate groups at position 4 of the pyrazolo[3,4-*b*]pyridine bicyclic core. Totally, 18 novel derivatives were synthesized and screened for their cytotoxic activity against PC-3 and HCT116 cancer cell lines. Four of these compounds showed potency less than 10μM and underwent extensive evaluation for the determination of their IC_{50} values, that proved to range between 0.75-4.55 μM. It is noticeable that the substitution pattern of the most active analogues is in direct agreement with their potency. An investigation of the mechanism of action of this novel class of compounds is currently in progress by our group.

Acknowledgments

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IMINORIBITOL-MODIFIED 3,4-DIARYL-ISOXAZOLES AS POTENT INHIBITORS OF CK1δ/ε

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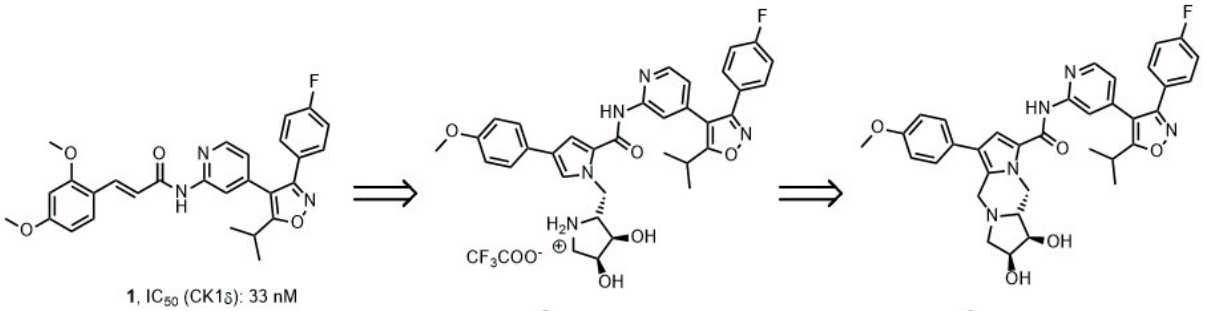
Casein kinases (CK) [1,2] are serine-threonine protein kinases that are conserved in eukaryotic organisms. They phosphorylate a high number of substrates and play important roles in the regulation of multiple cellular processes, such as cell division, apoptosis, membrane transport, immune response, inflammation, DNA repair, circadian rhythm, Wnt signalling, etc. Deregulation and dysfunction of CK1-isoforms including CK1δ/ε have been associated with proliferative disorders, such as cancer, and neurodegenerative diseases, such as Alzheimer's or Parkinson's disease, as well as sleeping disorders. Therefore, inhibition of CK1-isoforms has become an attractive target for therapeutic application. Highly desirable are isoform-selective kinase inhibitors because these will lead to reduced toxicity and improved efficacy, but creating such inhibitors is very challenging as kinase active sites are very similar. However, building inhibitors from scaffolds with inherent chirality may confer otherwise unachievable binding selectivity toward the highly homologous kinase domains.



Here we present the modification of the previously reported 3,4-diaryl-isoxazole-based CK1 inhibitor **1** [3] with enantiopure iminoribitol scaffolds to enhance its activity and selectivity. Guided by molecular modeling the pharmacophore of the lead inhibitor **1** was extended to the more hydrophilic areas of the ATP binding site to enable selective interactions. Biological evaluation of the designed inhibitors in CK1δ/ε *in-vitro* kinase assays revealed compound **2** and analogs thereof as potent inhibitors with IC_{50} values in the nanomolar range. Selectivity profiling of compound **2** in a panel of 320 kinases showed that its activity was quite specific for CK1. However, the impact of the different stereoisomers towards affinity and CK1 isoform-selectivity was minor. X-ray crystallographic analysis of a ligand-CK1δ complex to study the possible binding mode of our target compounds however, uncovered the presence of a new ligand (**3**) which, to our surprise, was formed by spontaneous Pictet-Spengler cyclization with traces of formaldehyde during co-crystallisation procedures. This new ligand and its enantiomer were found to be more potent than the originally designed target compounds.

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BIOLOGICAL EVALUATION OF NEW SMALL-MOLECULE ANTHRAQUINONE-BASED DERIVATIVES

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Anthraquinones also called anthracenediones are important members of the quinone family and have often been associated with undesirable properties. Derivatives of anthracene have proved to be promising bioactive compounds with a broad spectrum of activities including anticancer in various types of tumors (1).
One of the prevailing trends in designing new potential anticancer drugs is a modification of the dithiocarbamate core. However, the impact of this fragment on the biological activity remains unclear (2,3). With this view, in the present work, we attempt to explain the molecular mechanism of new 9,10-anthracenedione derivatives by in vitro and in vivo based assays.

Our results indicate that compounds showed antiproliferative activity in non-small cell lung cancer at micromolar concentrations and inhibit colony forming of cells in a short time treated. We observed slightly changes in the cell cycle distribution and cell morphology. Next, we estimated inhibiting telomerase activity concentration by TRAP assay and determined the ability of new derivatives to activate DNA double-strand breaks (DSB) by immunofluorescence and flow cytometry via tumor lines that differ in telomere elongation mechanism. Compounds activate DSB in TERT-positive A-549 cell line, highlighted by the increased levels of γH2AX. This effect was not observed in treated TERT-negative HUVEC cell line and in ALT-positive U2OS cell line, which indicates telomerase inhibition dependent induction of DSB.

These data demonstrate that novel dithiocarbamates have the potential to be further developed into novel anticancer chemotherapeutic agents.

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LONG CHAIN β-LACTONES: DESIGN, SYNTHESIS AND ANTIMYCOBACTERIAL ACTIVITY

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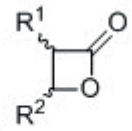
β-Lactones are compounds that include the strained 2-oxetanone 4-membered ring which is responsible for their activity as potent inhibitors of the serine/cysteine hydrolase class. Tetrahydrolipstatin, the most representative member of this family of inhibitors, is an FDA approved anti-obesity drug that acts as an irreversible inhibitor of human digestive lipases by covalently binding to their active site. *Mycobacterium tuberculosis* is the causative agent of tuberculosis and today, more than a century after its identification, it remains the leading cause of death due to a single infectious agent according to the World Health Organization. Many serine/cysteine hydrolases play an essential role in mycobacteria and especially in their cell wall and mycolic acid biosynthesis and maintenance. Efficient and selective inhibitors of such enzymes that may impair their activity appear to be an interesting alternative strategy not only in the fight against tuberculosis, but also against other mycobacterial infections. We herein report the design, synthesis and antimycobacterial activity of a series of long and medium chain substituted β-lactones.



R^1,R^2 : H, alkyl, alkenyl

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DEVELOPMENT OF NOVEL IRREVERSIBLE RHODESAIN INHIBITORS AS ANTITRYPANOSOMAL AGENTS

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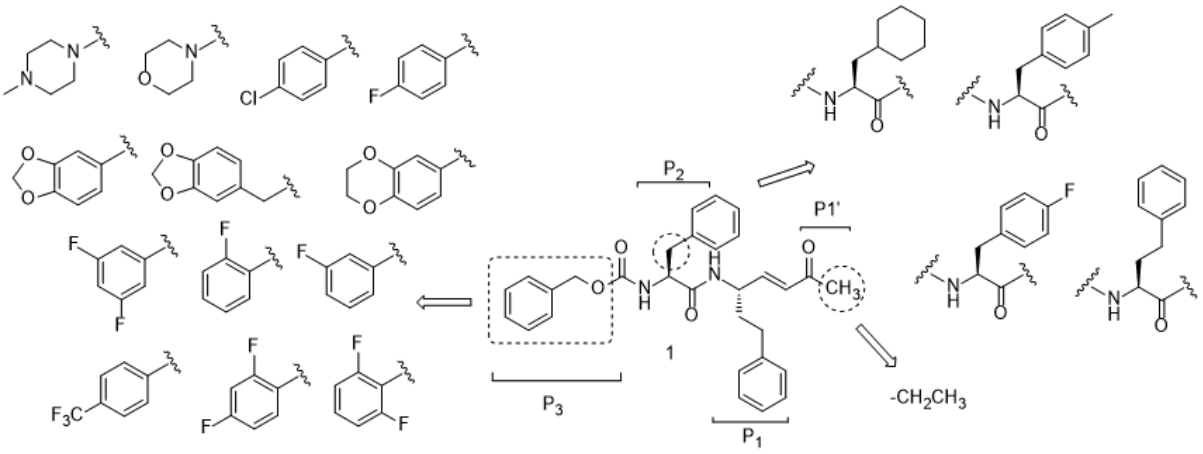
Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, is an endemic parasitic disease caused by two subspecies of *Trypanosoma*, *T. brucei gambiense* and *T. brucei rhodesiense*. It affects 36 countries of sub-Saharan Africa, where it continues to be an important cause of morbidity and mortality, mainly in the rural areas, in spite of the significant decrease in the number of new reported cases over the last years.[1] Rhodesain, a cysteine protease of *T. brucei rhodesiense,* represents one of the most valuable targets for the development of new antitrypanosomal agents. The importance of rhodesain is due to its several functions: it is required to cross the BBB, inducing the neurological stage of HAT; it is involved in the turnover of the VSGs of trypanosome, which forms a densely packed coat surrounding the parasite, whose periodic antigenic variation allows the parasite to evade the host immune system. In addition rhodesain takes also part to the degradation of parasite proteins and intracellularly transported host proteins within the lysosomes.[2]

Recently, we identified the dipeptidyl derivative **1**, an irreversible inhibitor of rhodesain, showing a high binding affinity (K_i = 38 pM).[3] Starting from the structure of lead compound **1**, we synthesized a new series of Michael acceptors in which the vinyl ketone warhead and the homophenylalanine at the P1 site were kept unchanged, whereas structural variations were carried out at P1', P2 and P3 positions (Fig.1). Starting from the lead compound **1**, we developed a panel of new molecules, as depicted in Figure 1.



The results of the biological investigation against rhodesain and *T. b. brucei* as well as molecular modelling studies will be reported and discussed.

Acknowledgments: S.M. acknowledges the support of "Programma Operativo Fondo Sociale Europeo (FSE) Regione Siciliana 2014–2020 – Asse 3 Ob. 10.5" for her PhD fellowship.

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BENZOXAZOLE-BASED ANALOGS OF VORINOSTAT AS POTENT CYTOTOXIC AGENTS

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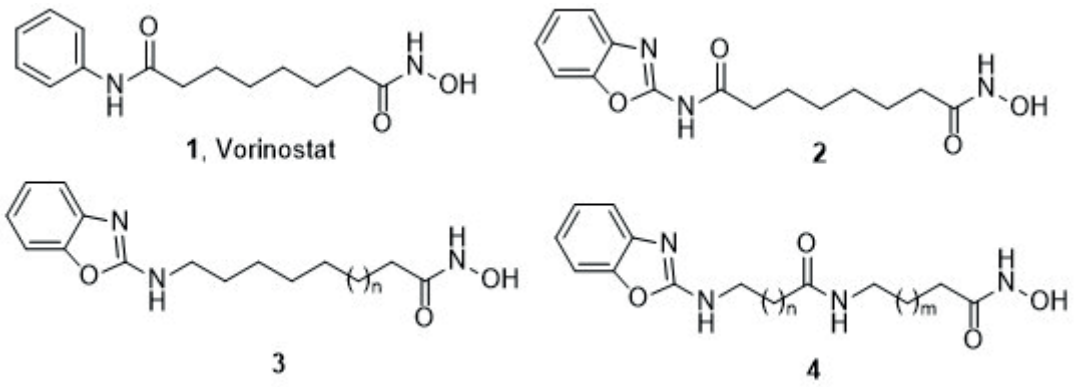
Numerous studies to date have indicated that histone deacetylase (HDAC) inhibitors represent a new class of anti-cancer agents [1]. Vorinostat (**1**, suberoylanilide hydroxamic acid or SAHA, trade name Zolinza) is a potent HDAC inhibitor and has been approved for the treatment of relapsed or refractory cutaneous T-cell lymphoma (CTCL), a type of cancer that attacks the immune system [2].

Based on the fact that benzoxazole derivatives are compounds that often exhibit various biological effects such as anti-proliferative or anti-microbial activity [3], a series of hydroxamic acid analogs of vorinostat containing the benzoxazole moiety, were designed and synthesized. The desired compounds were easily prepared by short synthetic sequences. Starting from commercially available unnatural amino acids and suberic acid, an assortment of amino acid methyl esters and suberic acid methyl ester were prepared and then coupled with benzoxazole and amino-benzoxazole, respectively. Amination of benzoxazole with amino acid methyl esters was carried out using tetrabutylammonium iodide, tert-butyl hydroperoxide and acetic acid at 50 ^{0}C. The resulting products were converted into hydroxamic acids **2**, **3** and **4** by treatment with hydroxylamine hydrochloride and sodium ethoxide in ethanol.

An MTT assay was conducted to assess the in vitro cytotoxicity of these compounds on three diverse cancer cell lines (A549, SF268 and Caco-2) using vorinostat as a reference drug. Several of the compounds synthesized in this work exhibited IC_{50} values comparable to those of vorinostat.



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BIOPHYSICS AND STRUCTURAL BIOLOGYFOR THE SOSA APPROACH: DEVELOPMENT OF HASPIN INHIBITORS VIA THE OPTIMIZATION OF THE SIDE ACTIVITY OF PIM1 INHIBITORS

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With the aim of testing our drug discovery tool-box to identify therapeutic relevant compounds, PIM1 was selected as target of choice. PIM1 is a serine/threonine kinase involved in leukemia, lymphoma and prostate cancer, but also in pulmonary hypertension. PIM1 has a recognized role in T cell development and has been implicated in the pathogenesis of autoimmunity.

The initial hits were first identified by SPR μarray screening of the immobilized ligand collection, then they were confirmed by native-MS for the binding and by biochemical assay for the activity. The elucidation of the binding mode by X-ray crystallography allowed the design for a rapid optimization of the initial hits: only 2 rounds of optimization were necessary to go from μM to single digit nanomolar compound ETB0087 (9 nM) against PIM1. ETB0087 turns out to have a nice selectivity profile against 358 kinases with an interesting activity against Haspin. Indeed, Haspin is an interesting target for oncology as the only Haspin substrate is threonine 3 of histone 3 thus inhibition of Haspin might have fewer adverse effects compared with other anticancer agents. Consequently, ETB0087 was taken as a good starting point for the development of Haspin inhibitors. X-ray crystallography studies of ETB0087 with PIM1 and with Haspin, revealed ETB0087 binds differently towards the hinge regions of these 2 kinases. A molecular descaffolding was successfully applied to a Selective Optimization of Side Activities (SOSA) approach of PIM1 selective lead molecules, affording novel fragment hits for Haspin. These were progressed into chemically novel sub-nanomolar leads on Haspin that are currently undergoing pharmacological exploration as tool compounds.

STUDIES BY DOCKING AND MOLECULAR DYNAMICS FOR DUAL 5-LOX/COX-2 INHIBITORS: DIFFERENCES BETWEEN TO THE BINDING INTERACTION IN BOTH ENZYMES AND SYNTHETIC ISOFLAVONOIDS

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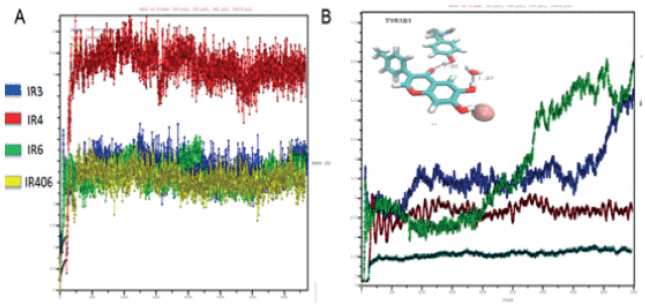
Using Docking and Molecular Dynamics (MD) studies, was possible to observe that for the COX-2 enzyme the modification on B ring of the isoflavone had no impact on the position or interaction to the ligand inside to the active site, but the modification of the catechol group on ring A, was the most relevant modification observed in the four molecules studied, presenting a common interaction with TYR386,[1] being a key residue for the activation of COX-2 and could explain why all ligands would have similar values of IC_{50} in biological assays. Regarding the analysis of the results of docking versus 5-LOX, these showed that the modification on B ring of each ligand was a key structural feature in the orientation and interaction in the active site, especially with the residue HIS600,[2] a residue that fulfills the function of orienting and directing the substrate within the catalytic site. Regarding the presence of the catechol group in the 5-LOX inhibitors in ring A, this turned out to be an important factor in the inhibition, since the modification of this resulted in the total loss of its capacity as an inhibitor of the enzyme. As mentioned above, the importance of the non-hemic iron atom in the catalytic site lies in the fact that the activity of the enzyme depends on the oxidation state of said metal, therefore, one of the most common mechanisms of inhibition, is the reduction of the oxidation state Fe (III) (active state of the enzyme), to Fe (II) that would correspond to the inactive state.[3] By means of docking and MD, two of the most powerful molecules studied showed the proper orientation of the catechol group towards the iron atom, and also through MD studies, the presence of a molecule of H2O was observed, which catalyze the change of the oxidation state of the metal and the subsequent inhibition of the 5-LOX enzyme.



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BIS(TRIAZOLYLPYRENE)-DERIVED PSEUDOPEPTIDES: SYNTHESIS, FLUORESCENCE PROPERTIES AND IN SITU FORMATION OF NANOAGGREGATES IN CELLS

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Self-assembled peptide nanostructures are very promising biomaterial with huge potential in several biomedical applications.[1-2] Pyrene is one of the most useful fluorogenic unit because of its high detection sensitivity. Formation of the self assembled complex results in a remarkable change in the fluorescence emission intensities of the pyrene excimer and monomer.[3] Due to their many interesting fluorescence properties, such as long lifetime, high quantum yield, and the possibility to form excimers, pyrene and its derivatives are of considerable interest for the development of sensors and diagnostic tools.[4]

In aim of design of fluorescent organic nanoparticles, novel products containing pyrene chromophore linked via a triazole ring to an amino acid derivatives were synthesised using Cu-catalized “click” reaction. We report the synthesis of novel bis(triazolylpyrene)-derived pseudopeptides, their photophysical properties, self-assembly in DMSO/H_2O as well as confocal fluorescence microscopy studies. Their bioactivity and cellular uptake will be tested on a panel of human tumor cell lines.

This work has been fully supported by Croatian Science Foundation under the project number IP-2016-06-5983.

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NOVEL CURCUMINOID ANALOGUES BEARING PYRAZOLINES: SYNTHESIS AND BIOLOGICAL EVALUATION

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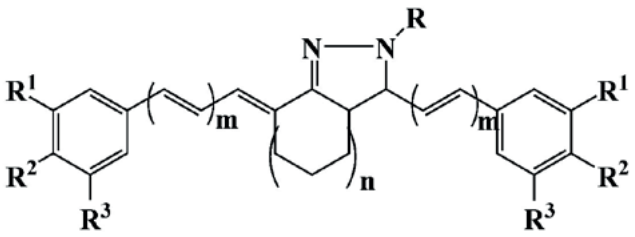
Curcumin (1,7-bis-(4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione), the main active constituent of turmeric, and other curcuminoids have been studied intensely in the recent years for potential pharmaceutical applications owing to their anti-inflammatory, antioxidant, anticancer, antibacterial and antifungal properties, among others [1]. However, chemical and metabolic instability, poor biodistribution and generally weak pharmacokinetic profile, partially attributed to the β-diketone moiety, prompted the scientific community to attempt structural modifications of these molecules by replacing the β-diketone moiety with a monocarbonyl one [2]. This new type of monoketone analogues exhibit in many cases up to 10–20 fold increased potency of biological action, better pharmacokinetic profiles, and less systemic toxicity in mice compared to curcumin. Further derivatization of the monoketone curcuminoid analogues can generate novel substituted pyrazolines. The pyrazoline moiety represents a structural component of significant interest in the field of Medicinal Chemistry, due to its prominent pharmacological profile, which includes antimicrobial, antimycobacterial, antifungal, antiamoebic, anti-inflammatory, analgesic, antidepressant, and anticancer activities.

With the rationale to take advantage of the diverse and tunable properties of the pyrazoline heterocycle to further enhance the pharmacological profile of natural and synthetic curcuminoids, in this work, the synthesis, structural characterization and biological evaluation of a series of curcuminoid analogues bearing pyrazolines, of the general formula shown below, is presented. Starting from commercially available materials, the novel functionalized pyrazolines were prepared via the corresponding curcuminoid intermediates with high purity and yields, as a result of the continuous optimization of the synthetic procedure and were characterized by NMR and X-ray crystallography. The synthesized derivatives, including a series of their metal complexes with Pt and Ag, were evaluated as potential anticancer agents showing promising activity at the nanomolar level against the MCF-7 breast cancer cell line. Furthermore, they exhibited high affinity for the Aβ plaques of Alzheimer' s disease, prompting us to further evaluate their potential as β-amyloid plaque imaging agents. The antimicrobial activity of these novel molecules against bacterial strains and fungi is also under investigation.



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FACILE RING CLEAVAGE OF BENZOCYCLOBUTENES TRIGGERED BY STAUDINGER REACTION AND ITS APPLICATION FOR NOVEL BIOORTHOGONAL REACTION SYSTEM

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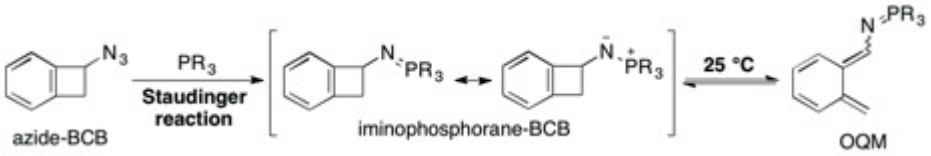
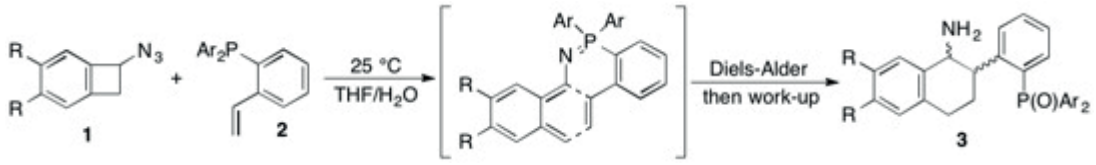
Thermal cleavage of benzocyclobutenes (BCB) via a 4p-electrocyclic process generates *o*-quinodimethanes (OQM), and most BCBs are known to require high temperatures of over 100 °C for the ring opening.[1] On the other hand, BCBs possessing an electron-donating substituent on the sp^3 carbon have been reported to have lower energy barriers toward OQM formation.[2,3] In this context, we envisioned that iminophosphorane-BCBs would generate OQMs under mild conditions due to the strong electron-donating nature of their anionic resonance structures, and that the iminophosphorane would be easily generated *in situ* through the Staudinger reaction of azide-BCBs. After careful experiments, we could prove the significant acceleration effects of the iminophosphorane substituents for the ring cleavage (at 25 °C).



For application of the above reaction system, we intended to trap the OQM intermediate by intramolecular Diels-Alder (IMDA) reaction employing styryl phosphine **2** as a dienophile. When the azide-BCB **1** was reacted with the styryl phosphine **2** in dry THF at 25 °C for 24 h, the desired sequential reaction, composed of Staudinger reaction/4p-ring opening/IMDA reaction, proceeded to afford cycloadduct **3** in 61% yield (R = MeO), even in the presence of water (36%). Moreover, when using azide-BCB **1** (R = H), the same reaction sequence gave the adduct **3** in 92% (without H_2O) and 67% (with H_2O) yields, respectively. We are considering that these findings may be applicable for development of novel bioorthogonal reaction system.



Further efforts to improve this reaction system are currently underway, and the details will be disclosed.

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SYNTHETIC SMALL MOLECULES INTERFERING WITH ONCOGENIC MICRORNAS FOR THE INDUCTION OF GLIOBLASTOMA STEM CELLS DIFFERENTIATION

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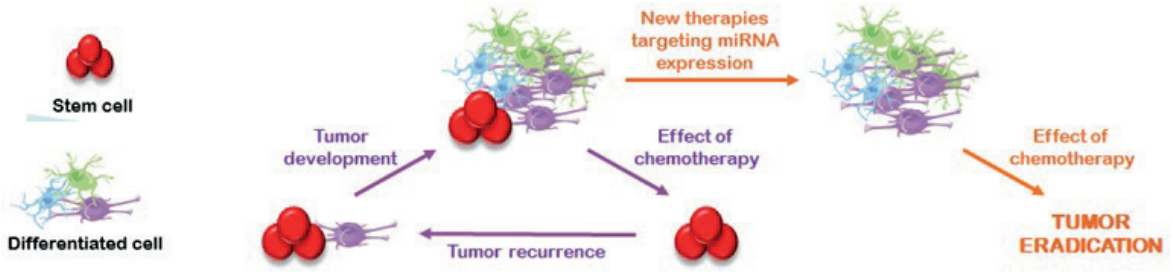
Glioblastomas (GBM) are the most common form of primary brain tumors afflicting adult patients of all ages and inevitably lead to a fatal outcome in less than 18 months. These highly vascularized and infiltrating tumors are resistant to current therapies which combines surgery, radiotherapy and chemotherapy with Temozolomide as alkylating agent.[a] They are constituted by different type of cells including GBM stem cells (GSCs) and differentiated cells ruled by the differentiation/dedifferentiation process. The resistance to treatments and tumor recurrences has been attributed to the presence of GSCs, which remain persistent and even more aggressive following conventional cytotoxic treatments.

A complex network of small non-coding RNAs, named microRNAs, is involved in the plasticity of GSCs and two main strategies have been described so far to target miRNA expression.[b] We chose indirect strategies, based on the use of multimodal small-molecule drugs to modulate miRNA expression by targeting their transcription and processing. [c] Recently, our team identified original compounds able to interfere with miRNAs biogenesis, some of them induce GSCs differentiation, inhibit clonal proliferation and strongly increase the sensitivity of these cells to Temozolomide.[d]



The purpose of this research project is to develop new drug to increase GSCs sensitivity to current chemotherapies by interfering with the microRNAs network. To date, we already synthesized a first series of derivatives bearing chemical modifications at various positions and identified the first structure-activity relationships using in vitro studies. The biological assays on primary glioblastoma cultures are currently in progress. From the achievement of this project, we expect the identification of druggable compounds for anti-GSC strategies bearing an extremely original mechanism of action and directed toward a so far incurable cancer.

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OATD-01 – ORALLY BIOAVAILABLE, DUAL CHITINASE INHIBITOR AS A POTENTIAL THERAPY FOR INTERSTITIAL LUNG DISEASES

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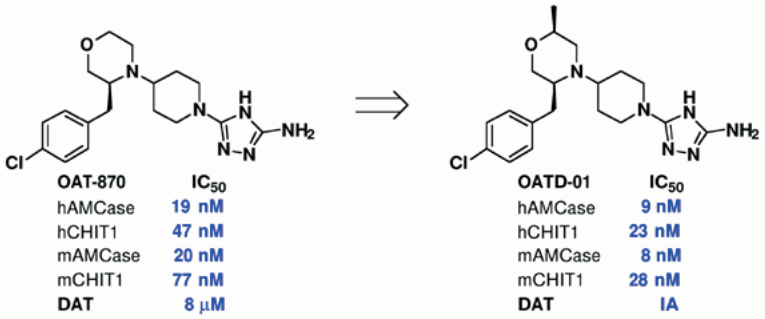
Acidic mammalian chitinase (AMCase) and chitotriosidase (CHIT1) are the enzymatically active chitinases, which have been shown to be involved in various lung pathologies such as idiopathic pulmonary fibrosis (IPF), sarcoidosis, chronic obstructive pulmonary disease and asthma. Elevated CHIT1 levels and activity were found in serum and bronchoalveolar lavage (BAL) fluids from patients with interstitial lung diseases (IPF and sarcoidosis). AMCase is activated during type 2 inflammatory responses in both murine models of airway inflammation and in asthma patients.

Compound **OAT-870** represents an advanced lead with optimized *in vitro* pharmacological profile in terms of inhibition of chitinases. Introduction of “magic” methyl in position 2 of the morpholine ring resulted in the elimination of activity against dopamine transporter (DAT) that was identified as a potential liability of **OAT-870**. The resulting inhibitor **OATD-01** demonstrated significant therapeutic efficacy *in vivo* in two mouse models: the anti-inflammatory effects in house dust mite (HDM) induced airway inflammation model as well as the anti-fibrotic therapeutic efficacy, comparable to pirfenidone, in the bleomycin-induced pulmonary fibrosis model. These data indicate that inhibition of chitinases activity may be considered as a novel therapeutic strategy for interstitial lung diseases. **OATD-01** is currently in phase Ib clinical trials.



CHEMOPROTEOMICS-AIDED PHARMACOPHORE REPURPOSING

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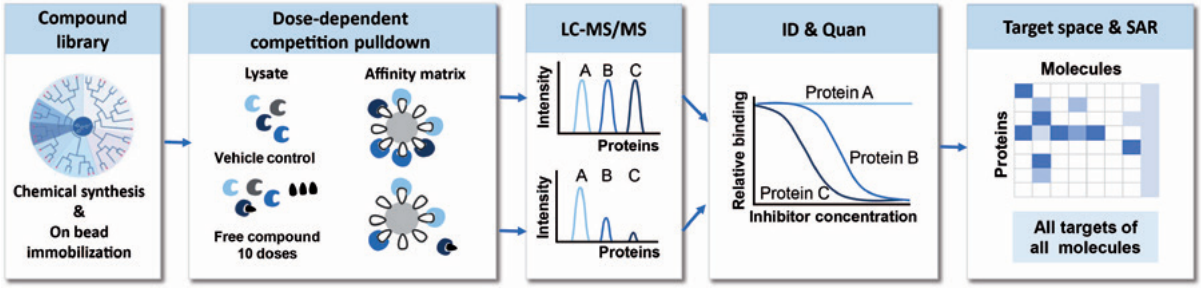
Proteomics pipelines allow for the simultaneous quantification of thousands of proteins contained in a biological material by mass-spectrometry. When a molecule or an analogue thereof is used as an enrichment probe, it becomes possible to perform unbiased target deconvolution by extracting its native targets out of a biological material. We are using this principle to decipher the target space of small molecules or natural compounds against proteomes.



We profile in particular kinase[1] and HDAC inhibitors, for which we have designed family-specific affinity matrices. We here report on a novel generation of Kinobeads which allow to also profile PIK(K) inhibitors.[2] Moreover, we have obtained a matrix for the zinc-dependent lysine deacylases which for the first time allow to investigate class IIa HDAC inhibitors by chemical proteomics (manuscript in preparation). With those matrices and the chemical proteomics approach, off-targets of known drugs have been evidenced, allowing for drug repurposing hypotheses. For instance the ATM inhibitor CP466722 has been found to be a native wild-type ALK2 binder, and confirmed to also inhibit its mutated isoform responsible for most cases of *fibrodysplasia ossificans progressiva.*Its intra-ALK family selectivity makes it an interesting new chemotype for this disease.[2]

Additionally, structure-affinity relationships as well as structure-selectivity relationships of pharmacophores have been established by systematic chemoproteomic target deconvolution of sets of novel analogues. We have in particular repurposed Dasatinib scaffold to obtain a cell-active more selective EPHA2 inhibitor.[3] This concept holds immense promises in the early identification of pharmocophore repurposing opportunities, particularly for human or parasite yet-to-drug targets.

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ProteomicsDB: A BIG-DATA, MULTI-OMICS, MULTI-ORGANISM RESOURCE FOR LIFE SCIENCE RESEARCH

Patroklos Samaras (1), Tobias Schmidt (1), Pia Bothe (1), Martin Frejno (1), Siegfried Gessulat (1,2), Jana Zecha (1), Anna Jarzab (1), Maria Reinecke (1), Julia Mergner (1), Piero Giansanti (1), Johannes Rank (3), Harald Kienegger (3), Helmut Krcmar (3), Hans-Christian Ehrlich (2), Stephan Aiche (2), Guillaume Medard (1), Bernhard Kuster (1,4), Mathias Wilhelm (1)

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ProteomicsDB (https://www.ProteomicsDB.org) is an in-memory database initially developed for the exploration of quantitative human mass spectrometry-based proteomics data. By integrating protein turnover data, protein melting properties, transcriptomics data, cell viability results, drug selectivity data, protein-protein interaction information, functional annotations and experimental and predicted reference mass spectra, ProteomicsDB has transformed into a multi-omics, multi-organism resource. Integration of these data contributed to the development of a novel human tissue ontology based on multi-omics expression patterns **enabling users to investigate drug responses and to predict drug sensitivity or resistance of stored or uploaded proteomics or transcriptomics expression data.** Furthermore, we recently extended the data model to support data from other organisms, and extended ProteomicsDB's functionality to *Mus musculus* and *Arabidopsis thaliana*.

ProteomicsDB's new data model in combination with the RDF-like triple-store framework enables the integration and fast querying of different omics data from different organisms, by storing different resource identifiers in an object-oriented way. The MComBat normalization scheme is applied to enable the interconversion of different omics expression measurements. This also allows the integration of custom user expression data alongside with stored expression data. Elastic net models have been trained on cell viability data, which can be applied on user-uploaded expression profiles, to predict drug responses on the selected samples. Consensus clustering on multi-omics expression profiles was used for the establishment of a tissue ontology based on molecular similarity, to allow drug enrichment analysis for treatment suggestion.

ProteomicsDB is transforming into a multi-omics and multi-organism platform that enables the storage, visualization and analysis of data across multiple omics datasets of different tissues, cell lines and fluids from multiple organisms. To date, **ProteomicsDB stores more than 10^7 and 10^8 protein and transcript expression values across >200 tissues, 10^6 dose-response curves covering ~1.500 kinase inhibitors, 10^7 cell viability curves across 667 drugs and 1.467 cell lines, ~6.000 protein turnover rates, >13.000 melting protein curves,** 10^7, 10^6 and 10^7 experimental, synthetic reference and predicted mass spectra totaling 10^{10} fragment ions. Furthermore, the integration of cell viability data with proteomics or transcriptomics expression values in ProteomicsDB, led to the generation of **>10^6 elastic net models, predicting sensitivity and resistance of cell lines upon drug treatment.** Because of the newly implemented normalization scheme, users can upload and normalize custom expression data and predict the viability of their biological material for every drug available in ProteomicsDB. A newly developed feature is the molecular human tissue ontology, which is generated based on the molecular fingerprint of tissues and cell lines rather than their localization in the human body. Users can browse this new ontology or co-cluster their uploaded expression data in order to check for e.g. drug sensitivity and resistance profiles. In addition, we have imported proteomics and transcriptomics expression data for *Mus musculus* and *Arabidopsis thaliana* covering 41 and 30 tissues and ~17.000 and ~18.000 proteins, respectively. Inherent to ProteomicsDB's design, all analytical functions (e.g. expression heatmap, normalization methods, response plots), are automatically available, allowing the straightforward extension to all other supported data types. For example, we have added predicted and acquired reference spectra from the ProteomeTools and Prosit projects for all identified mouse and arabidopsis peptides, directly available in the appropriate website sections.

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SMALL MOLECULE MODULATION OF THE NUCLEAR RECEPTOR RORγt VIA A NOVEL, ALLOSTERIC BINDING SITE

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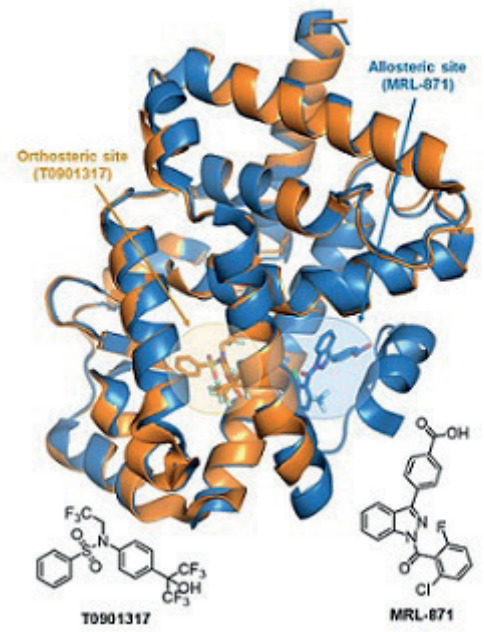
Nuclear Receptors (NRs) are a large family of transcription factors in the human body, controlling several essential functions of the cell such as metabolism, development and reproduction. The retinoic acid receptor-related orphan receptor (ROR) is a subclass of these NRs which demonstrates high therapeutic potential, in particular the RORγt isoform. RORγt is expressed in lymphoid organs such as the thymus, where active RORγt is required for the differentiation and proliferation of T helper 17 (Th17) cells.[1,2] The inappropriate activation of Th17 cells has been linked to the pathology of numerous autoimmune disorders. The inhibition of RORγt by use of small molecules could therefore represent a promising strategy for the treatment of autoimmune diseases.[3]

Most of the reported modulators target the orthosteric binding site in the ligand binding domain (LBD) of RORγt. However, recently a novel type of inverse agonist (MRL-871) was explored. As observed in the co-crystal structure, this compound occupies an alternative, previously undisclosed binding site in the LBD of RORγt, called allosteric site.[4] Binding to this site results in repositioning of Helix 12 towards a less stable state, preventing the binding of co-activators and therefore leading to inhibition, similar to orthosteric inhibition. This allosteric modulation could be advantageous over orthosteric modulation in terms of selectivity issues and mutation-induced resistance.

Following this, we have further explored the allosteric binding pocket of RORγt. We present the design and synthesis of novel allosteric ligands with pharmaceutical potential, the physiological effect of allosteric inverse agonists in cells, the design of covalent orthosteric ligands that could be used to permanently block the orthosteric site and the synthesis of a bivalent ligand occupying both the orthosteric and allosteric site of RORγt.



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PRE-CLINICAL DEVELOPMENT OF A NOVEL ORAL TREATMENT FOR MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is an autoimmune, demyelinating and neurodegenerative disease. Treatment options are not effective in all disease variants, and have side effects that cause abandonment of treatment and, consequently, disease progression. In addition to the immune cell infiltration, the pathology of MS is related to exacerbated oxidative stress that in turn induces an aggravated inflammatory process causing the development of new lesions observed in the disease. Therefore, novel medicinal chemistry strategies are directed to reduce oxidative stress and decrease the neuroinflammatory process observed, as key targets that could halt the disease progression.

Based on these observations, our drug discovery program led to the identification of an Nrf2 inducer with neurogenic properties, compound PM122, as possible drug candidate for the treatment of MS. However, the chemical instability of the compound hindered its preclinical development. To overcome this drawback, we have modified the structure of compound PM122 in order to ameliorate its drug-like properties. The pharmacological evaluation of the novel derivative PM162 showed that the compound preserves the activities on the targets described for compound PM122. In addition, compound PM162 showed and excellent safety profile. Also the pharmacokinetic profile of compound PM162 has been studied.

Finally, we have evaluated compound PM162 in an *in vivo* model of MS, the EAE model. Preliminary *in vivo* results showed ability of compound PM162 to reduce the score of the disease in orally treated mice, thus reinforcing compound PM162 is a novel potential oral treatment for MS.

EXPLORING THE DETERMINANTS OF ISOFORM-SPECIFIC INHIBITION OF CK1 KINASES BY THE USE OF ADVANCED THEORETICAL SIMULATIONS

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The group of Casein kinase-1 (CK1) proteins includes Ser/Thr protein kinases that are highly conserved within eukaryotes. Numerous cellular processes considered as of pivotal importance are regulated by different CK1 isoforms (α, γ1, γ2, γ3, δ and ε in human) such as the Hedgehog and Wnt signaling pathways, DNA replication and repair, circadian rhythms and cytoskeleton maintenance. At present, CK1 proteins are regarded as highly attractive drug targets for a wide array of pathologies spanning from neurodegenerative diseases and sleep disorders to cancer. However, the existence of several isoforms renders selective CK1 inhibition a challenging endeavor and to this respect, isoform-relevant inhibitors can greatly contribute either to the direction of developing drug candidates that possess an optimally designed pharmacological profile or for facilitating exploration of the extent that each different CK1 isoform contributes to a specific phenotype. In the present study we report the use of a consensus ranking *in silico* screening algorithm implementing a variety of orthogonal theoretical methods including structure-based docking-scoring simulations in addition to ligand-based three- and two-dimensional screening tools for assessing the CK1 inhibition potential of the NCI-Diversity set II. Experimental evaluation of the complete compound collection validated the novel consensus ranking approach as an efficient tool for improving the screening hit rate and afforded a quinoline derivative, NSC45572, as a potent and highly promising CK1 inhibitor (IC_{50} of 1.5μM, CK1δ). Subsequently, the effect of this specific compound was investigated *in vitro* against several CK1 disease-related isoforms and a highly original selectivity profile was identified. To provide a structural and thermodynamic explanation for the observed selectivity, a series of sophisticated molecular modeling methods such as MM/PBSA calculations, advanced Molecular Dynamics and metadynamics simulations, QM-based approaches and hydration mapping were implemented. The findings suggest that whereas selectivity is determined by a number of different factors, the design of isoform targeting inhibitors is feasible and can be greatly accelerated by rational drug discovery methodologies.

STRUCTURAL CHARACTERIZATION OF NUCLEOBASE TRANSPORTER UAPA USING METADYNAMICS

Iliana ZANTZA (1), Simone AURELI (2), Stefano RANIOLO (2), George LAMBRINIDIS (1), George DIALLINAS (3), Vittorio LIMONGELLI (2,4), Emmanuel MIKROS* (1)

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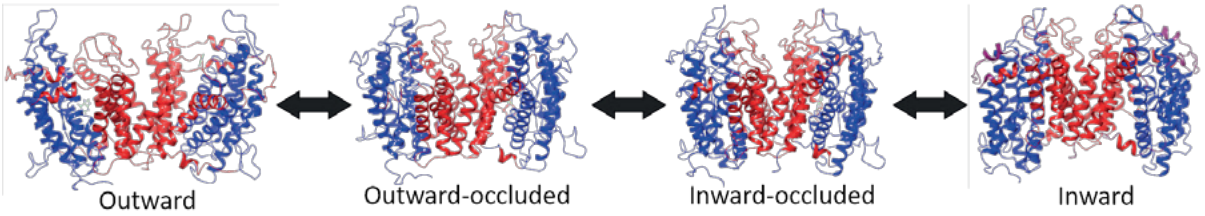
Transmembrane transporters are proteins mediating the selective uptake or efflux of solutes, metabolites, drugs, or ions across cellular membranes. Among them, NCS2/NAT proteins are H^+ or Na^+ symporters responsible for the uptake of purines, pyrimidines or related metabolites in bacteria, fungi and some plants. In particular, the UapA transporter of *Aspergillus nidulans* is specific for the transport of xanthine and uric acid in the fungi cells. While *A.nidulans* is harmless for humans, *A.fumigatus*, another member of the *Aspergilli* family, is the most common airborne fungal pathogen and can cause severe and usually fatal invasive infections in immunocompromised hosts. For this reason, elucidating the molecular mechanism of the *A.nidulans*' transporters is important to illustrate how to exert an exogenous control of its activity, thus paving the way to the development of anti-fungal drugs.

UapA works as a dimer, each unit consisting of 14 transmembrane segments folded in a rigid core domain and a flexible gate domain. Its biological function is based on a transportation mechanism called "elevator", which implies the relative motion of the gate domains sliding on the core. The entire transportation process can be divided in four protein states: Outward-Open (OOp), Outward-Occluded (OOc), Inward-Occluded (IOc), and Inward-Open (IOp). The endogenous ligand approaches the dimer from outside the cell to the OOp conformation, which progressively evolves into the IOp conformation allowing the molecule to enter the cytoplasm. Importantly, a crystal structure of the IOp conformation was recently resolved and several mutations have been reported, identifying key residues in the transportation mechanism. However, the exact translocation pathway remains elusive and the transportation mechanism is still unclear.

In this project, the objective is to reproduce the "elevator" mechanism from the OOp to the IOp state of the protein, by employing cutting-edge metadynamics simulations. In this way, we aim to correlate computational and experimental data and gain insight into this large-scale and complex phenomenon. Structures of the missing steps in the translocation pathway, namely OOp, OOca and IOc states, were built using targeted MD simulations starting from the UapA pdb (PDBID 5I6C) and using as template the crystal structures of the homologous transporters Band3, Bor1, UraA, respectively. A Path Collective Variable defined in the space of the root main square deviation of selected protein's backbone atoms was chosen to reproduce the large-scale conformational changes of the core-gate domains. Interestingly, we observed in the simulation an asynchronous behaviour of the dimers, in which they undertake the transportation mechanism only one per time. Furthermore, simulating the Xanthine in the binding site with the receptor in the IOp state, we found that Gln 408 plays a key role in the ligand unbinding, confirming data previously reported in literature. In particular, its flexibility allows to lead the ligand throughout most of the transportation process and deliver it to Arg481, which finally releases the molecule inside the cell.



DISCOVERY AND FUCTIONAL CHARACTERIZATION OF SELECTIVE CYSTATHIONINE BETA SYNTHASE INHIBITORS IDENTIFIED THROUGH RATIONAL APROACHES AND HIGH-THROUGHPUT SCREENING

Anna Maria Fantel (1), Vassilios Myrianthopoulos (1), Anastasios Georgoulis (2), Aggeliki Tsoka (2), Nicole Pouli (1), Marakos Panagiotis (1), Constantinos E. Vorgias (2), Antreas Papapetropoulos (1), Emmanuel Mikros* (1)

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Cystathionine beta synthase, CBS, is a unique PLP depended enzyme that has been identified as a major contributor to hydrogen sulfide production. CBS is overexpressed in many different tumor types, resulting in cancer-specific characteristics and hence it represents an attractive drug target. Human colorectal cancer cells contain high levels of CBS and recent studies show that CBS is also implicated in the pathogenesis of ovarian and breast cancer. Thus, selective inhibitors of hCBS are of importance for both further investigations of H_2S signaling and the development of novel treatments of H_2S-related disease states. The enzyme exhibits a modular organization and complex regulation. This study presents an integrated approach for developing potent and selective CBS inhibitors by using a combination of *in silico* and *in vitro* techniques. The human CBS enzyme was expressed in *E. coli* as GST fusion protein and *in vitro* high throughput screening was performed using a colorimetric assay (methylene blue assay). Approximately 500 compounds rationally selected from various different libraries were tested against CBS and the IC_{50} values of the most potent modulators were calculated by dose-response curves. The most active compounds are synthetic molecules bearing a pyrazolopyridine scaffold derived from the NKUA compound collection. Most potent inhibitors exhibited comparable activity to AOAA, the most well described CBS inhibitor currently in use. The top performing compounds were subjected to molecular modeling calculations by using all important structural features of CBS (PLP binding Cavity, heme binding domain, allosteric domain) as well as to differential scanning fluorimetry, functional assays and enzyme kinetics for identifying the exact inhibitory mechanism of the new leads.

SYNTHESIS AND EVALUATION OF ANTI-MITOTIC ACTIVITY OF NOVEL 2H-PYRAZOLO[4,3-c]PYRIDINES

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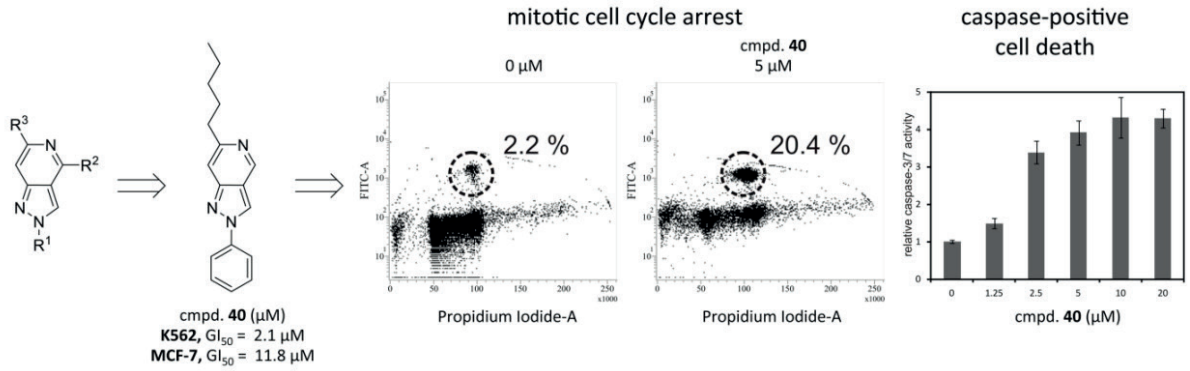
Organic heterocyclic compounds possessing pyrazole ring attract significant interest due to their various biological and pharmacological activities. In a series of recent publications, we have demonstrated that pyrazole-4-carbaldehydes, carrying an alkynyl function adjacent to the formyl moiety, are valuable starting materials for the construction of condensed pyrazole derivatives. The aim of this study was to synthesize 2*H* -pyrazolo[4,3-*c*]pyridines, primarily varying by the substituents at the 2-, 4- and 6-positions. Sonogashira-type cross-coupling reaction was employed to yield 3-alkynyl-1*H*-pyrazole-4-carbaldehydes, ethanones and propanones from the corresponding 1*H*-pyrazol-3-yl trifluoromethanesulfonates. Subsequent treatment of the coupling products with dry ammonia afforded a versatile library of 2*H*-pyrazolo[4,3-*c*]pyridines. Newly prepared 2*H*-pyrazolo[4,3-*c*]pyridines were evaluated for their cytotoxicity against K562 and MCF-7 cancer cell lines. The most potent compounds displayed low micromolar GI50 values in both cell lines.[1]



Acknowledgements: This research was supported by the Research, Development and Innovation Fund of Kaunas University of Technology (grant No. PP-91B/19) and by the National Program of Sustainability I, MEYS, IGA_PrF_2017_013 and IGA_PrF_2018_006 (grants No. LO1204 (Sustainable development of research in the Centre of the Region Haná)).

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SYNTHESIS OF MEDIUM-RING-CONTAINING HYDANTOINS THROUGH MIGRATORY RING EXPANSION OF METALLATED UREAS

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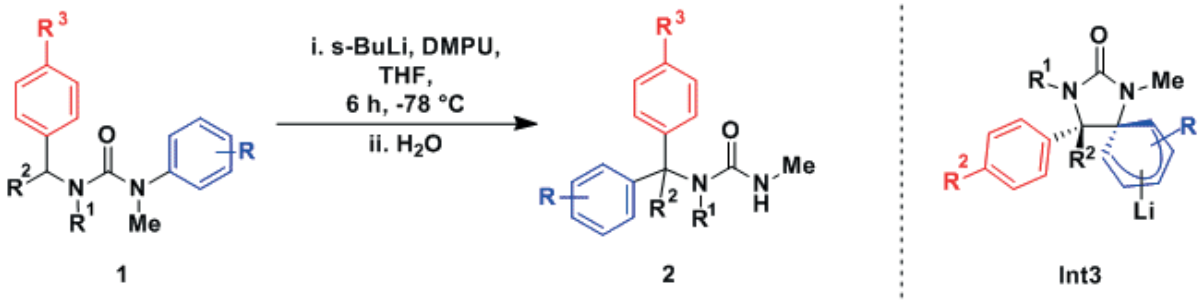
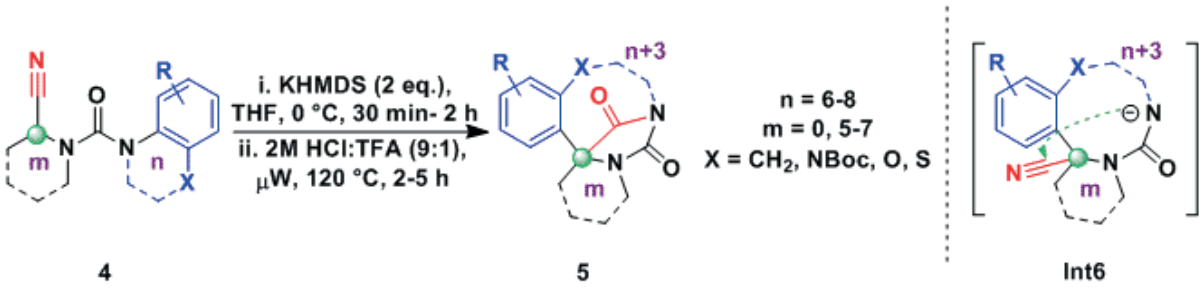
Hydantoin motifs are highly privileged medicinal chemistry scaffolds with hundreds of literature syntheses known; however few contain medium-rings (8-12 membered). [1-2] Medium-rings exhibit conformational constraints inferring elevated binding affinity to biological targets compared to linear structures, hence they are prevalent in medicinally relevant natural products but are lacking in marketed pharmaceuticals. [3] This scarcity is due to associated difficulties of their synthesis, thus there exists a need to develop new facile synthetic routes to medium-rings.



Scheme 1: *N to C* aryl migration of *N*-benzyl-*N'*-aryl ureas.

In 2007 the Clayden group first reported their discovery of intramolecular *N to C* aryl migration of *N*-benzyl-*N'* -aryl ureas (*Scheme 1*). [4] This remarkable transformation occurs in good yield irrespective of the electronic or steric nature of the substituents on the migrating arene. The reaction is formally an *ipso* S_NAr displacement. Treatment with base leads to a benzyllithium, which then adds to the "distal" aryl ring to give dearomatised intermediate **Int3.** Subsequent ring-opening under the reaction conditions or during work-up affords the diarylmethyl urea, **2.**



Scheme 2: Medium-ring containing hydantoin synthesis through migratory ring expansion.

This work utilises the intramolecular *N* to *C* aryl migration shown in *Scheme 1.* Tethering the migrating group (shown in blue) to the nitrogen leads to medium-ring formation (**5**) through *n to n+3* ring expansion upon deprotonation as shown in *Scheme 2.* Attack of the nitrogen anion to the anion-stabilising nitrile (**Int6**) forms the iminohydantoin. Hydrolysis of the iminohydantoin with acid furnishes the desired medium-ring containing hydantoins, **5** in predominantly good to excellent yield over two steps.

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ENABLING SUCCESS IN LEAD IDENTIFICATION- DEVELOPMENT OF A HTS LIBRARY AT SYGNATURE DISCOVERY

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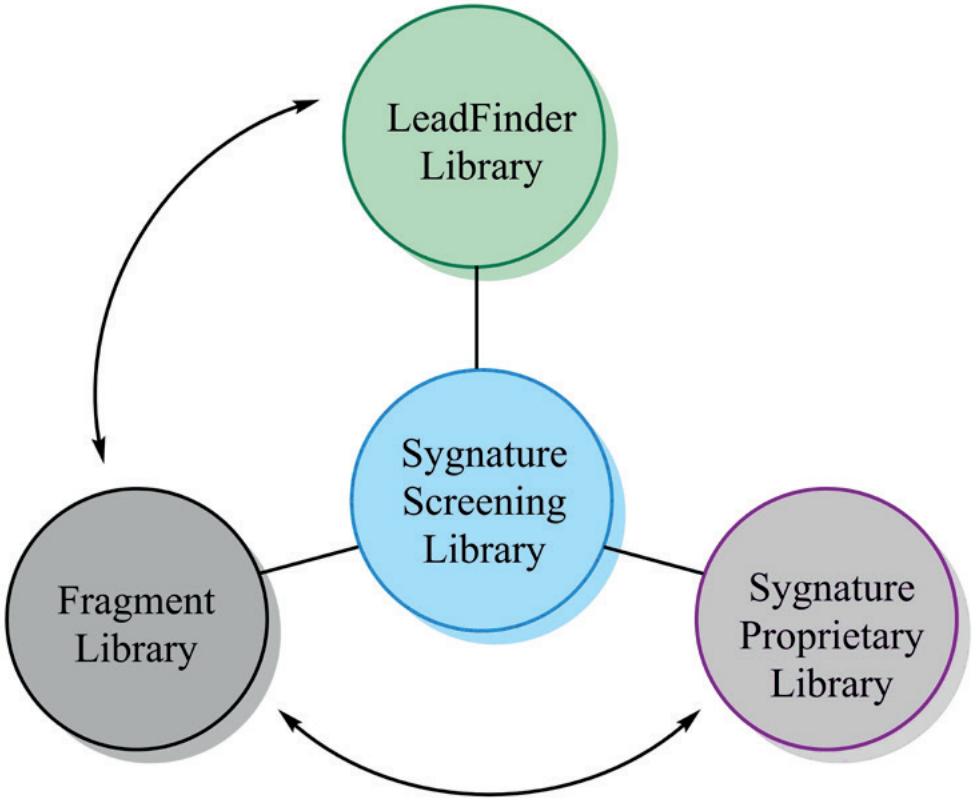
A crucial part of identifying novel leads is the diversity and suitability of the molecules to be screened which in turn will determine the likelihood of obtaining viable chemical starting points for new projects. How do you strike the balance between compound diversity and the ability to rapidly validate and select the most promising hits for follow up?

In this poster we will share our view on the strategies for building compound libraries that maximise the probability of identifying tractable hit series for a range of target classes. Having created multiple compound libraries which have been selected and filtered computationally but also assessed individually by experienced medicinal chemists we present our experience in the selection and synthesis of compounds to provide highly relevant lead-like starting points for client projects.



DISCOVERY OF NOVEL MYCOBACTERIUM CELL DIVISION INHIBITORS TARGETING FTSZ - A MODELLING & EXPERIMENTAL STUDY

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Tuberculosis has been one of the primal afflictions to human. In addition owing to the current scenario of drug resistance, clearly newer drugs and alternate targets are required to mitigate the disease. FtsZ is a GTPase that plays prime role during cell division process. It is a homolog of tubulin sharing less than 10% sequence identity and is conserved among prokaryotes due to which it is attracting attention as a possible target for drugs. This study employs the use of pharmacophore models derived from unique datasets comprising of reported Mtb-FtsZ GTPase inhibitors, to virtually screen and identify novel compounds from In-house small molecule library and evaluate their *in-vitro* activity. The results revealed a Pharmacophore model that is predominantly hydrophilic bearing one aromatic and two acceptors which identified, Piperine (IC_{50}= 21.2 ± 0.7 μM), 4-Bromo di-methoxy coumarin (IC_{50}=13.0±1.6μM) and Di-ethyl amino methyl coumarin (IC_{50}= 19.4 ±1.1 μM) to exhibit good Mtb-FtsZ GTPase inhibition, and they also possess antibacterial activity against *Mycobacterium smegmatis* with MIC_{90} of 84.0±2.6 μM, 56.0±4.3 μM and 108 ±7.1 μM respectively. In addition Aloin from *Aloe* species were found to show good Mtb-FtsZ GTPase inhibition (IC_{50}=16.7 ± 0.4 μM) but poor anti-mycobacterial activity (MIC>500 μM). Docking studies revealed that the mapped pharmacophoric points were interacting with the critical residues of enzyme active site. Treatment with these compounds lead to aberrant 4X increase in cell length of *M.smegmatis,* implicating a phenotypic response of FtsZ inhibition.

NEW FRONTIERS FOR THE ANTIBIOTIC RESISTANCE STRUGGLE

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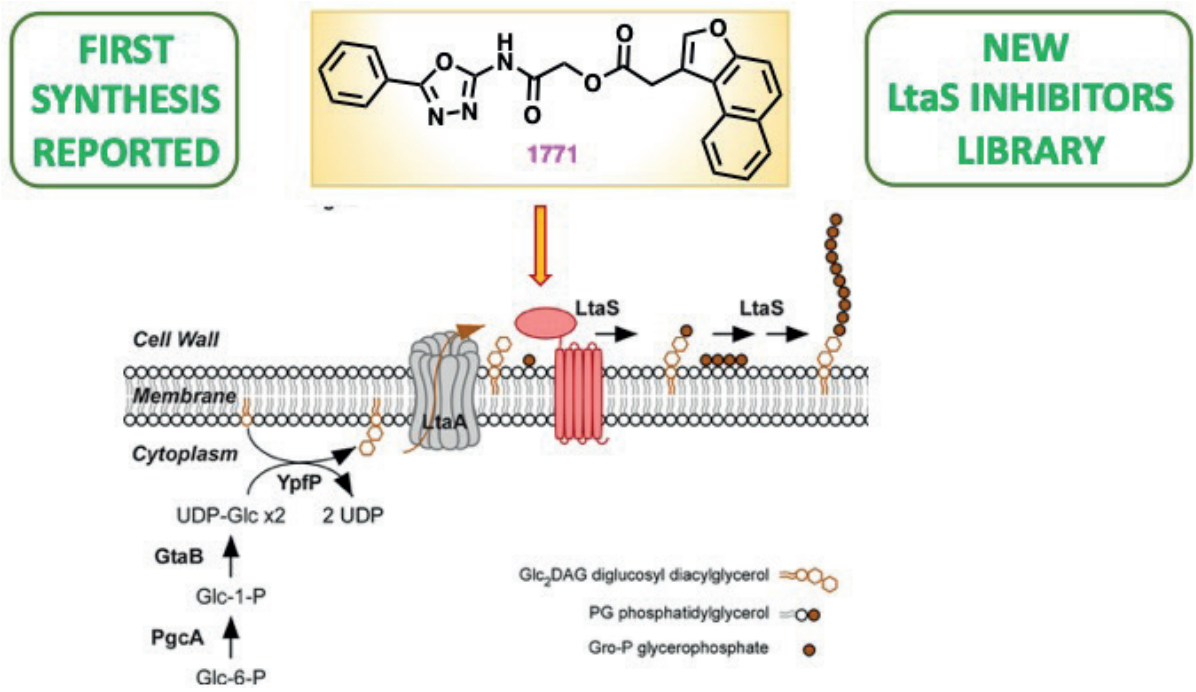
Antibiotic resistance phenomena (AMR)[1]is one of the major scientific issues of modern times and it is estimated that by 2050 microbial infections will cause 10 million people to die every year unless a global response to AMR is mounted.[2] Among multi-drug resistance Gram-positive bacteria, *Staphylococcus Aereus,* causes a significant number of life-threatening hospital and community acquired infections and therefore, it has been designated by the WHO as a high priority pathogen for the development of new antibiotics. *S. Aureus* produces also biofilms on medical devices (e.g. catheters), which are densely packed communities of microbial cells highly resistant to clearance by antibiotics and the body's natural defenses. A specific enzyme namely lipoteichoic acid synthase (LtaS), involved in the biosynthesis of *S. aureus* lipoteichoic acids (membrane glycopolymers responsible for its growth, survival and biofilms formation), was recently validated as novel target for antibiotics using compound 1771, a LtaS inhibitor.[3] Here, we reported the first synthesis of compound 1771 as well as its stability studies in buffer at different pHs and in biological matrix. On the basis of its degradation pathways, we have designed more stable analogues using both rational and computer-aided drug design.



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IDENTIFICATION, SYNTHESIS AND OPTIMIZATION OF INHIBITORS OF THE PROTEIN TYROSINE PHOSPHATASE SHP2

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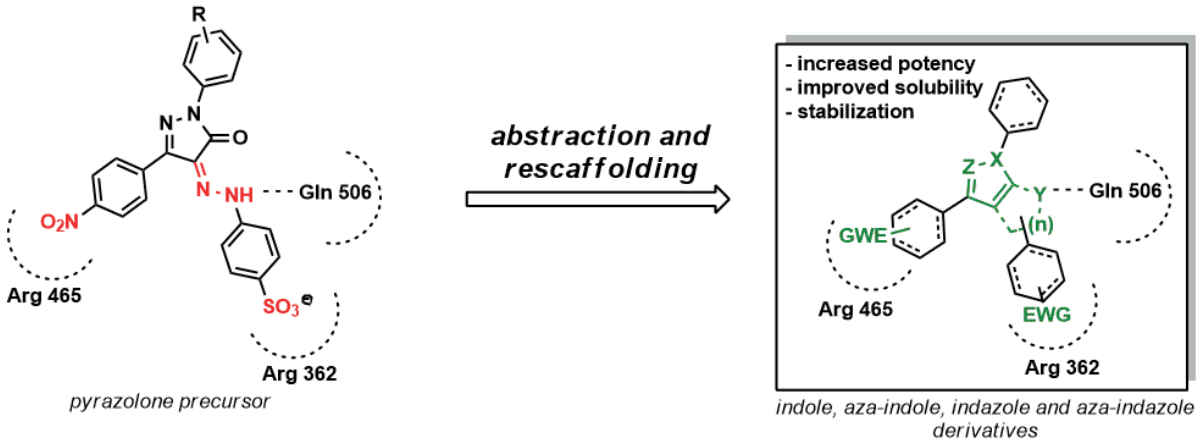

pyrazolone precursor

indole, aza-indole, indazole and aza-indazole derivatives

Protein tyrosine phosphorylation and de-phosphorylation are key events in cellular signal transduction and are often aberrant in cancer. The non-receptor tyrosine phosphatase SHP2 (the PTPN11 gene product) mediates growth factor and cytokine signals and regulates the activity of the Ras-MAPK pathway. The oncogenic function of mutated SHP2 is related to sustained activation of Ras/MAPK signaling and SHP2 is widely up-regulated in infiltrating breast carcinomas. SHP2 activity is linked to acquired drug resistance to medications targeting MAPK-pathway (like MEK and BRAF inhibitors)[1]. It was demonstrated, that the pharmacological inhibition of SHP2 suppresses mammary gland tumor development by reducing cancer stem cells. In a previous study, using a virtual screening effort with a database of 2.7 million compounds using a homology model of SHP2, the lead structure PHPS1 was identified as a highly active and selective pyrazolone derived SHP2 inhibitor[2]. However, this compound class bears three unwanted, non-druglike structural features: (i) a nitro group (ii) a sulfonic acid (iii) and a hydrazone based scaffold. In general, the presence of these functional groups accounts for chemical and metabolic liability, cytotoxicity as well as low cell permeability. Here we report the development of very potent, selective and in particular drug-like inhibitors of SHP2 by replacing these unfavorable structural features by a rescaffolding of the core unit and searching for bioisosteric substitutes of the unwanted fragments.

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DISCOVERY OF LIGAND STRUCTURE-ACTIVITY RELATIONSHIP BY MASS SPECTROMETRY: IDENTIFICATION OF NEW TUBERCULOSIS INHIBITORS

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A set of tuberculosis fragment inhibitors has been discovered by mass spectrometry. The method is based on the observation of protein-ligand complexes by mass spectrometry.[1] These fragments may compete for common binding sites on the target protein or bind at different sites. Mass spectrometry enables identification of ternary complexes in which two ligands bind to different sites of a target.[2-3]

For a specific target, the result $(P+L_1) + (P+L_2)$ indicates binding to the same site (competitive), while the result $(P+L_1) + (P+L_2) + (P+L_1+L_2)$ shows that L_1 and L_2 bind to different sites (non-competitive). Compound design relies on using a number of competitive fragments linked to a non-competitive fragment. In the next step, the structures of these fragments will be modified using synthetic methods to enhance their activities and produce novel inhibitors.

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SATURATED HYDROXY FATTY ACIDS: A NOVEL CLASS OF CYTOTOXIC AGENTS

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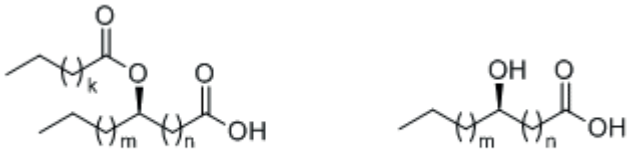
Fatty acids and closely related glycerolipid molecules are fundamental structural components, serving as a major energy reservoir, as well as precursors of a range of signaling molecules. In recent years, they have also turned out to play a role in the direct regulation of metabolism and inflammation through activation of free fatty acid receptors. Although several polyunsaturated hydroxy fatty acids are known for their ability to act as potent signaling mediators, less is known for the bioactivity of saturated hydroxy fatty acids (HFAs). Some HFAs are relatively common; 2-hydroxy fatty acids are abundant in sphingolipids, and 3-hydroxy fatty acids are found as intermediates in fatty acids synthesis. Recently, fatty acid esters of hydroxy fatty acids (FAHFAs), mainly composed of saturated fatty acids, have emerged as a novel lipid class reported to exhibit anti-inflammatory and anti-diabetic properties [1]. On the other hand, racemic hydroxy lauric acids have been reported to interact with free fatty acid receptors FFA1, FFA4 and GPR84 [2].

We have recently reported a convenient enantioselective general methodology for the asymmetric synthesis of FAHFAs and HFAs [3]. Herein we present the application of this methodology for the synthesis of various saturated HFAs and the evaluation of their in vitro cytotoxicity against cancer cell lines. The key step of our methodology consists of the organocatalytic synthesis of asymmetric terminal epoxides using mono-protected α,ω-diols as starting materials and MacMillan's third generation imidazolidinone as a catalyst for the induction of chirality. The formation of the epoxide and the subsequent epoxide ring opening using a Grignard reagent allows choosing the position of the hydroxyl group of the fatty acids. Use of both diastereomers of MacMillan's catalyst enables the synthesis of both *(R)*- and (*S*)-HFAs in high enantiomeric purity.

The in vitro anti-proliferation activities of the compounds synthesized were studied against diverse cancer cell lines (A549, Caco-2, U87-MG, SF268) applying cell viability assays. (*R*)-Enantiomers were proved more potent than the (*S*)-ones, while the position of the hydroxyl drastically influences the in vitro potency. Among the compounds tested, 7-*(R)*-hydroxy-stearic acid was found to exhibit the highest potency.



(*R*)-FAHFAs **(*R*)-HFAs**

Acknowledgements: The support from the "Special Account for Research Grants" of the National and Kapodistrian University of Athens is gratefully acknowledged.

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PYRROLIDINE AND 2-PYRROLIDINONE DERIVATIVES AS AUTOTAXIN INHIBITORS

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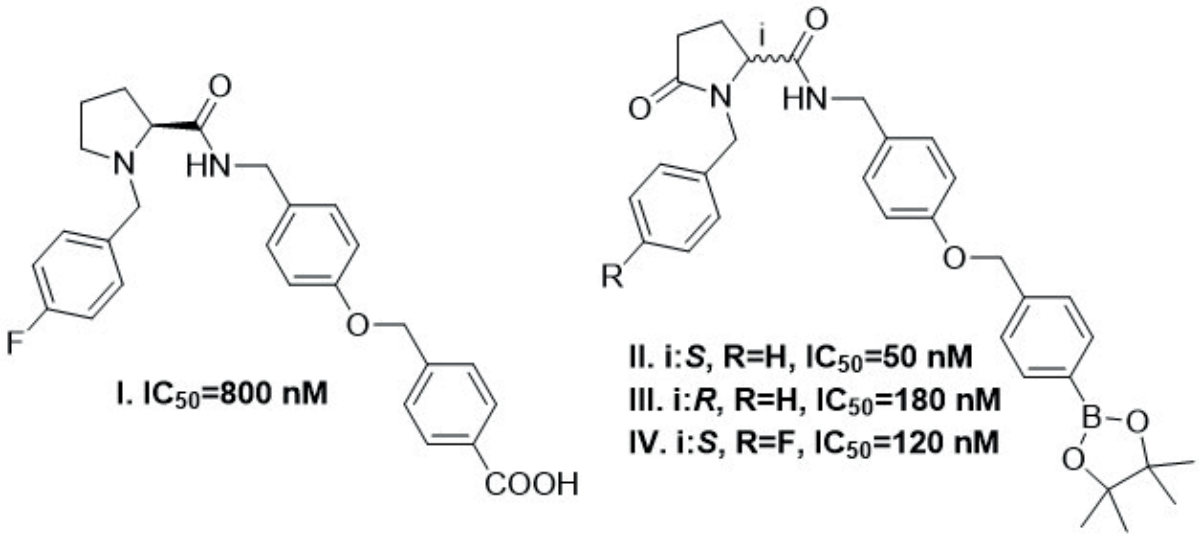
Autotaxin (ATX) is a glycoprotein that belongs to the family of ectonucleotide pyrophosphatase/phosphodiesterase enzymes.[1] ATX is a secreted enzyme, which catalyzes the hydrolysis of lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA) and choline. LPA is a bioactive lipid mediator, which binds to specific G-protein receptor and activates signal transduction pathways such as migration, proliferation and cell growth. Both ATX and LPA are involved, under physiological conditions, in the development of neural system, brain and embryonic development. Furthermore, ATX and LPA have been implicated in pathological processes, including tumor growth and metastasis, neuropathic pain, atherosclerosis, pulmonary and hepatic fibrosis and chronic inflammatory disorders. Consequently, ATX is established as an attractive target for the development of potent inhibitors.[2,3] In this work, we present the synthesis of new optically active derivatives of either pyrrolidine or 2-pyrrolidinone, starting from the natural amino acid (*S*)-proline or (*R*/*S*)-pyroglutamic acid, respectively. The latter is a widely used chiral synthon, found in the formula structure of many drugs (i.e. S-Vigabatrin, Indolizine A58365, Lactacystin etc).[4] All synthesized derivatives were tested for their *in vitro* activity on recombinant mouse ATX using the Amplex Red PLD assay kit (Molecular Probes, Interchim, Montlucon, France) and LPC (16:0) as substrate. The carboxylic acid derivative I exhibited interesting *in vitro* inhibitory activity of ATX, while the boronic acid derivatives II, III, IV were proved to be potent inhibitors of ATX.



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SYNTHESIS, BIOLOGICAL EVALUATION AND IN SILICO STUDIES OF STRUCTURAL ANALOGUES OF (Z)-3-(PENTADEC-10'-ENYL)-CATECHOL, A POTENT INHIBITOR OF 5-hLOX BY MIXED INHIBITION ISOLATED FROM THE EPICUTICULAR EXTRACT OF LITHRAEA CAUSTICA

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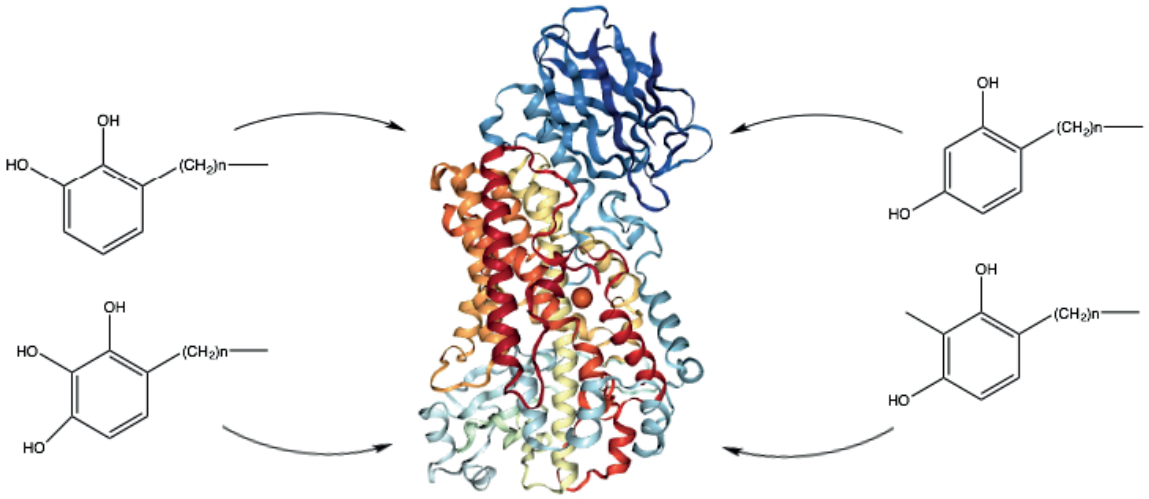
LOXs are a family of enzymes that contain a non-heme iron as central atom, in state of oxidation ferric the enzyme is active and ferrous the enzyme is inactive [1]. They catalyze the di-oxygenation of polyunsaturated fatty acids [2] and play an essential role in the biosynthesis of leukotrienes, lipoxins and physiologically active oxygenated fatty acids.

In addition, lipoxygenases regulate the pathophysiology of various diseases such as allergies and inflammatory reactions, among others [3]. Plants with anti-inflammatory properties would be related to the inhibition of the activity of this family of enzymes.

This research presents the synthesis, *in vitro* and *in silico* studies of new structural analogues of (Z)-3-(pentadec-10'-enyl)-catechol, a potent inhibitor of 5-hLOX isolated from the epicuticular extract of *Lithraea caustica*. The objective is the study of the influence on the variation of the length of the lateral alkyl chain and the substitution on the aromatic ring for create new active compounds against 5-hLOX.

Preliminary studies of structural analogues shown that as the length of the side chain increases, an increment in the affinity for the catalytic site of the enzyme 5-hLOX was observed. In addition, the modification of the substituents in the aromatic ring of resorcinol analogues showed a variation in the affinity with the catalytic site of the enzyme 5-hLOX.



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NOVEL ORGANOMETALLIC RHENIUM (I) AND IRON (II) COMPLEXES AS POTENTIAL INHIBITORS OF 5-hLOX. SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES

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One of the health problems that has remained in the course of time worldwide is the inflammation[1]. This process is a natural and defensive response of our body to different external stimulus. It is directly related to the development of various cardiovascular, respiratory, and inflammatory conditions, such as asthma, arthritis, psoriasis, infections, and arteriosclerosis[2,3]. In addition, inflammation can be harmful by attacking the tissues of our body, becoming chronic and persistent, being involved in the development of critical and/or neurodegenerative diseases such as Alzheimer's, Schizophrenia, Parkinson's and cancer[4,5]. 5-hLOX is one of the important proteins involved in the inflammatory process.

In general, the known inhibitors of 5-hLOX are organic derivatives, which cause side effects and resistance to the drug. Therefore, in recent years, the incorporation of a metallic center has been evaluated as a new strategy in the design of these potential polypharmaceuticals. A family of cyrhetrene ($CpLRe(CO)_3$ and ferrocene (FcL) complexes (L= H, CHO, COOH, NH_2) were synthesized. All complexes were fully characterized and were obtained as solids in high yields.

Subsequently, the biological activity of the organometallic complexes was evaluated *in vitro* in 5hLOX. Our findings suggest, in general, moderate activity in 5-hLOX. However, ferrocene carboxylic acid showed high activity with an IC_{50} of 2.53 ± 0,22 μM. Moreover, once all complexes were obtained a docking study between the organometallic complexes and the 5-hLOX protein were carried out (Figure 1). Our results are in agreement with the experimental data.

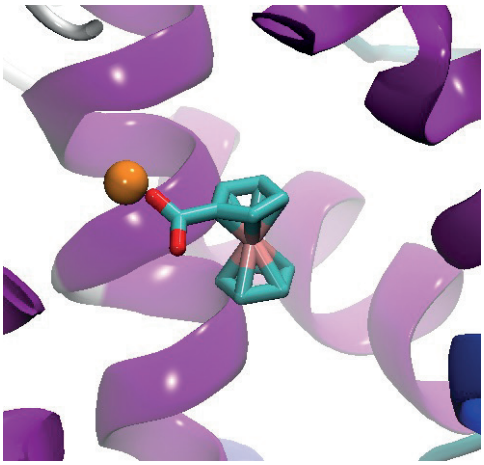

Figure 1. Docking study between ferrocene carboxylic acid and 5-hLOX.

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DEVELOPMENT OF A PROTEIN- PROTEIN-INTERACTION INHIBITOR TO HINDER THE UNCONVENTIONAL SECRETION OF THE POTENT MITOGEN FIBROBLAST GROWTH FACTOR 2

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Fibroblast Growth Factor 2 (FGF2) promotes tumor cell survival and tumor-induced angiogenesis in a number of different malignancies of both solid and hematological cancers [(1)], which makes it a good target for drug development. Since FGF2 secretion from tumor cells does not follow the conventional secretion pathway through the ER and Golgi apparatus, but an unconventional mechanism, the development of an inhibitor targeting this mechanism was attempted. The analysis of the unconventional pathway revealed FGF2 to directly translocate through the cell membrane. A number of factors were identified, that play a role in the secretion process and could be exploited as possible drug targets: Phosphoinositide (4, 5)- bisphosphate (PIP2) dependent membrane recruitment, phosphorylation through Tec kinase, FGF2 oligomerization to form a membrane pore and disassembly of the pore by heparan sulfate proteoglycans in the extracellular space[(2)]. A transient interaction of FGF2 with Tec kinase, while bound to PIP2, supports the oligomerization process through tyrosine phosphorylation. The influence of this interaction onto the secretion efficiency was shown by the identification of small molecules, which showed an effect on the direct protein-protein interaction, tyrosine phosphorylation in vitro and in vivo and on the secretion of FGF2 from cells. Through the optimization of these small molecule protein-protein interaction inhibitors with a SAR approach, compounds with a promising effect on the interaction could be identified.

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SYNTHESIS AND CHARACTERIZATION OF FLUORESCENT DERIVATIVES OF ANTITRYPANOSOMAL PAULLONES

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Among the worldwide disease burden, parasitic infections caused by protozoa remain one of the main contributors to fatalities in developing countries. Certain types of *Trypanosomatida* are human pathogens that cause a variety of vector-borne parasitic diseases, such as Chagas and sleeping sickness. While no vaccines are available to date, the current treatment options are limited and suffer from severe adverse effects and growing resistance.

The paullones, a family of protein kinase inhibitors, have been shown to exhibit antitrypanosomal activity by inhibiting TryS, a unique enzyme of *Trypanosomatida*.

Guided by molecular docking we have developed fluorescent derivatives by attachment of BODIPY fluorophores via linker chains to the paullone scaffold. These labelled compounds will be used to study the role and fate of antitrypanosomal paullones inside the parasite cell. The synthesis and the characterization of fluorescence properties will be reported in the presentation.

Support by the German Science Foundation (DFG Research Grant KU-1371/9-1) is gratefully acknowledged.

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FLUOLEAD, A VERSATILE AND SAFE NUCLEOPHILIC FLUORINATION AGENT

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Versatile, safe, shelf-stable and easy-to-handle fluorination agents are strongly desired in both academic and industrial arenas, since fluorinated compounds have attracted considerable interest in many areas, such as drug discovery, due to the unique effects of fluorine atoms when incorporated into molecules.

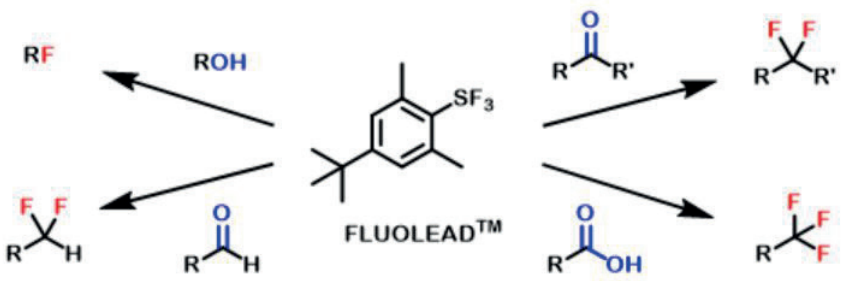
We have discovered and characterized 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (FLUOLEAD™), as a crystalline solid which has versatile fluorination capability as deoxo-fluorinating agent in addition to possessing high thermal stability and unusual resistance to aqueous hydrolysis, compared to traditional agents, such as DAST and its analogues (see table 1 below).

Table 1. Comparison of FLUOLEAD™ vs competitive products

Item		FLUOLEAD™	DAST	Deoxo-Fluor
Deoxo-fluorination for:	Ketone (enol form)	✓	✗	✗
	Carboxylic acid	✓	✗	✗
Decomposition temperature		High (260°C)	Low (140°C)	Low (140°C)
Sensitiveness to moisture		Low	High	High
Handling / Safety		Easy	Difficult	Difficult
Appearance		Solid	Liquid	Liquid

FLUOLEAD™fluorinates alcohols, aldehydes, ketones and carboxylic acids to give the corresponding monofluoro, difluoro, and trifluoro products (Scheme 1). The reaction conditions shall be acid, non-polar solvent and with catalysts e.g Pyridine-HF.

Scheme 1. Application of FLUOLEAD™ for deoxo-fluorination



To summarize, FLUOLEAD™ has a high thermal stability, is easy to handle and needs only one step for deoxo-fluorination. It is now available in large scale and UBE Industries will also be able to provide soon fluorinating technology under GMP.

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ARYL AND HETEREOCYCLIC SULFUR PENTAFLUORIDE (SF_5) COMPOUNDS, AS THE BEST ALTERNATIVE TO CF_3 GROUP

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Sulfur pentafluoride (SF_5) group is called "Super-trifluoromethyl (CF_3) group" [1], and the expected properties of SF_5-containing compounds are similar to the ones which are seen in general fluorine compounds, although most of them are significantly enhanced by the increment of the number of fluorine atoms in SF_5 group. Thanks to its high chemical and thermal stability, strong electron-withdrawing effect and outstanding lipophilicity, SF_5 group is the best alternative to CF_3 group and can be easily used as building blocks for pharmaceutical or agrochemical industries.

Electron-withdrawing Effect [2]

SF_5 group is recognized as a strong electron-withdrawing group. Table 1 below shows the comparative values of pKa in the substituted benzoic acid derivatives which have SF_5, CF_3, SCF_3, OCF_3 and F, respectively. SF_5 derivative is ranked as the second strongest group after the nitro-substituted one.

Table 1. Comparative values of pKa

Compounds						
pKa (EtOH:H_2O=50:50)	4.60	**4.82**	5.11	5.15	5.16	5.28
σ_m	0.73	**0.61**	0.44	0.40	0.39	0.28

Lipophilicity [1]

It is well known that compounds which incorporate fluorine(s) show greater lipophilicity. Table 2 shows the comparative values of lipophilicity with varying substituents in the molecule. SF_5substituted compounds are expected to show excellent lipophilicity compared with other fluorine-containing compounds.

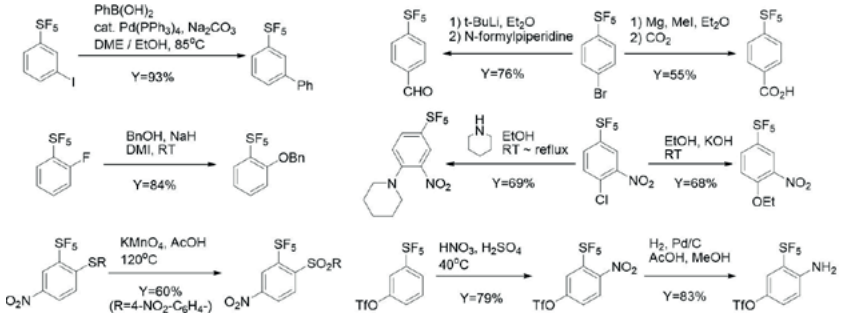
Table 2. Lipophilicity (p) of Substituent X

X	SCF_3	SF_5	OCF_3	CF_3	F	H	NO_2
π_p	1.44	**1.23**	1.04	0.88	0.14	0	-0.28

Application to Synthetic Chemistry

SF_5 groups are so stable that SF_5 containing compounds can be widely applied for common synthetic transformations in high yield.

Scheme 1: Examples of reactions for Aromatic SF_5 compounds



Please also note that heterocyclic-SF_5 compounds are currently under development and for all SF_5 compounds, UBE Industries will also be able to provide soon fluorination technology under GMP.

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DRUG CANDIDATE ABX464 AS A PROMISING NOVEL ANTI-INFLAMMATORY AND ANTI-HIV THERAPY

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Current therapies have succeeded in controlling AIDS pandemic. However, despite the successful control of viremia, many HIV-infected individuals treated with ART exhibit residual inflammation associated with non-AIDS-related morbidity and mortality. Thus, there is a continuing need for new drugs, in particular for ones acting through new and as yet unexplored mechanisms of action, which would ideally not only achieve HIV infection cure but also address the issue of the concomitant inflammation process.

A screening of the Curie-CNRS collection enabled the identification of a polycyclic indole compound which was shown to inhibit HIV-1 pre-mRNA splicing and to compromise the assembly of infectious particles.[1] To reduce the toxicity associated with this planar structure, hundreds of non-fused polyheterocyclic analogues were synthesized. Among several compounds selected for their interesting activities against HIV-1 replication, ABX464 demonstrated unique and very promising properties, such as a long-lasting reduction and control of the viral load in humanized mice.[2] Using chemical and imaging tools, its novel mode of action was elucidated and proceeds through binding to the Cap Binding Complex (CBC).

In further studies, ABX464 demonstrated strong anti-inflammatory effects in the DSS-model for inflammatory bowel disease (IBD).[3] Furthermore, ABX464 had no adverse effect on global pre-mRNA splicing in PBMCs, while it specifically modified HIV splicing. It was also found to increase the expression of a single microRNA, miR-124, inducing an anti-inflammatory response.[4]

Its nice safety and efficacy profile demonstrated in phase 2 proof-of-concept clinical trials in patients with ulcerative colitis or HIV, together with its specific dual ability to generate anti-inflammatory miR-124 and to prevent replication of the HIV, make ABX464 a first-in-class drug candidate with strong potential as innovative treatment of both inflammatory diseases and HIV infection.

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DESIGN AND SYNTHESIS OF DEHYDROEPIANDROSTERONE-BASED NEUROTROPHIN MIMETICS

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Neuro**t**rophins (NTs) belong to a family of secreted proteins associated by structure and function that bind with high affinity and selectivity to the **T**yrosine **R**eceptor **K**inases (TrkA, TrkB and TrkC), and exert powerful neuroprotective and neurogenic activity, both centrally and peripherally. Furthermore, they bind with low affinity to the **P**an **N**euro**t**rophin **R**eceptor **75** ($p75^{NTR}$), in contrast to their immature forms (pro-neurotrophins), which show high selectivity and affinity for $p75^{NTR}$. However, due to their polypeptidic nature, NTs are not suitable for therapeutic use. Thus, small druggable molecules, mimicking neurotrophin beneficial actions are highly desirable.[1]

The endogenous sex steroid precursor **De**h**y**dro**e**pi**a**ndrosterone (DHEA) is able to activate the neurotrophin receptor TrkA exhibiting neuroprotective activity,[2] while, it inhibits acute microglia-mediated inflammation.[3] We have recently synthesized 17-spiro-epoxy-dehydroepiandrosterone derivatives with anti-apoptotic and neuroprotective activity, selectively mediated through the neurotrophin receptors.[4-6] These compounds, in contrast to the parent molecule DHEA, are not metabolized to estrogens and androgens and exhibit high affinity for the NGF receptor, TrkA.

As a continuation of our studies on steroidal neurotrophin mimetics, we embarked on the synthesis of 17-spiro DHEA derivatives substituted by 6- or 5-membered rings, decorated with a variety of pharmacophores, in order to probe the stereo-electronic requirements for optimum neurotrophic/neuroprotective/neurogenic activity. Preliminary *in silico* studies were performed to examine the possible binding sites of the compounds to neurotrophin receptors.

The new derivatives were evaluated for their agonistic activity for TrkA, TrkB and $p75^{NTR}$, on NIH-3T3 -stable transfected with each receptor- cells, while, their anti-apoptotic activity was evaluated using the neural-crest-derived PC12 cell line. Moreover, their effect on inflammatory responses were tested in microglia cells.

Acknowledgement. This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 765704 (www.euroneurotrophin.eu).

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DISCOVERY AND PROFILING OF A HIGHLY POTENT AND SELECTIVE ERK5 INHIBITOR: BAY-885

Duy Nguyen, Clara Lemos, Lars Wortmann, Knut Eis, Simon Holton, Ulf Boemer, Dieter Moosmayer, Uwe Eberspaecher, Joerg Weiske, Christian Lechner, Stefan Prechtl, Detlev Suelzle, Franziska Siegel, Florian Prinz, Ralf Lesche, Barbara Nicke, Katrin Nowak-Reppel, Herbert Himmel, Dominik Mumberg, Franz von Nussbaum, Carl Nising, Marcus Bauser, Andrea Haegebarth

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ERK5 (Extracellular signal regulated kinase 5, also known as MAPK7, Gene ID: 5598) is a key integrator of cellular signal transduction and it has been shown to play a role in various cellular processes such as proliferation, differentiation, apoptosis and cell survival. Several studies have demonstrated that inhibition of ERK5 with siRNA or shRNA decreases proliferation and increases cell death in different tumor models, thereby highlighting the potential of ERK5 as a therapeutic target in cancer. By HTS and subsequent lead identification, we discovered a highly potent and selective ERK5 inhibitor, BAY-885, which was used to investigate the therapeutic potential of ERK5 in tumor cells displaying ERK5 genomic amplifications or with constitutive activation of the ERK5 pathway.

BAY-885 inhibited ERK5 enzymatic activity with IC_{50} = 40 nM and was highly selective vs. 357 kinases (Eurofins panel). Inhibition by BAY-885 was confirmed in a cellular setting using a MEF2 reporter cell line (SN12C-MEF2-luc). The EGF-stimulated MEF2 transcriptional activity was strongly inhibited by BAY-885 (IC_{50} = 115 nM; IC_{90} = 691 nM). In contrast, the compound had no effect on a reporter cell line with constitutive luciferase expression (SN12C-CMV-luc, IC_{50} > 50 µM), thereby ruling out potential effects as a general inhibitor of transcription or translation. Importantly, despite its high potency, BAY-885 failed to inhibit the proliferation of cells with ERK5 genomic amplification (SN12C, SNU-449, MFM-223) or with constitutively active ERK5 signaling (BT-474, SK-BR-3).

Altogether, our results demonstrate that inhibition of ERK5 kinase and transcriptional activity with a small molecule did not translate into antiproliferative activity in different relevant cell models, thus raising doubts as to the viability of ERK5 as a therapeutic target for anticancer drug development. The availability of potent and selective chemical probes, as the one described here, will contribute to further understanding the biology of ERK5 signaling in cancer.

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OPTIMIZATION OF NANOSTRUCTURED LIPID CARRIERS (NLC) WITH NATURAL SOY PHOSPHATIDYLCHOLINE AS A TOOL FOR ORAL TREATMENT

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Lipid nanocarriers are promising tool for delivery of lipophilic drug enhancing their bioavailability and they are employed in pharmaceutics and biomedical formulations (1). This study was focused on the optimization of the composition of nanostructured lipid carriers with natural soybean phosphatidylcholine (SBPC) as a component of surfactant phase to obtain stable nanoparticles dispersion using the high shear homogenization (HSH) method followed by ultrasonication.

To define optimal formulation of NLC a 2^3 full factorial design were used. Three independent variable were as follows: percent of liquid lipid in lipid phase (Miglyol® 812N), percent of soy phosphatidylcholine (Lipoid® S 100), percent of polysorbate 80 (Tween® 80), whereas the amount of lipids were fixed at 2%. The effects of the NLC composition on the mean particle size, polydispersity index and zeta potential were tested. NLC were produced using 24,000 rpm HSH for 2 minutes in 55°C followed by ultrasonication for 3 minutes.

Morphology was determined by TEM and revealed fairly spherical shape of NP. NLC were subjected to stability study and were stored either in 4, 20 or 40°C for 2 and 7 days. Lumisizer® analysis showed creaming phenomenon in NLCs formulations. Sample stored in 4°C were bigger in size and polydispersity but also more stable during centrifugation. Instability index were *ca.* 0,35 for samples stored for 2 and *ca.* 0,40 for 7days.

This factorial design study allowed to obtain NLC with small diameter (. The present results proved the usefulness of applying statistical design method in the optimization and preparation of lipid nanoparticles.

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PHOTOCHEMICAL OXIDATION OF ALCOHOLS UTILIZING AIR AS THE OXIDANT

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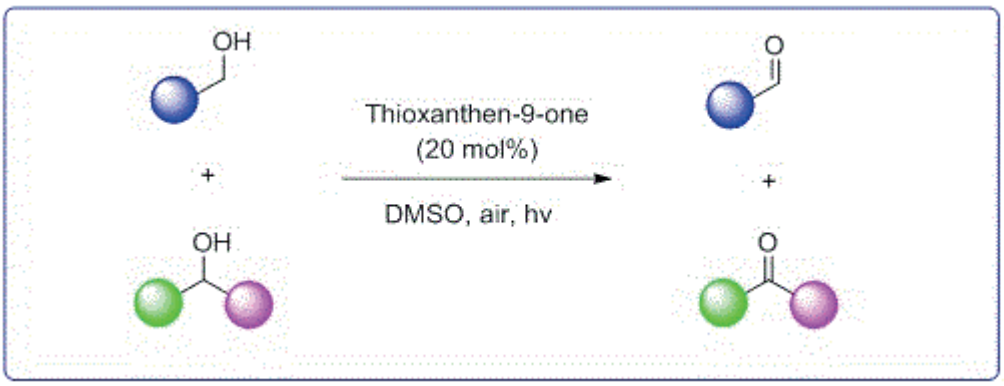
Photoredox Catalysis has brought a revolution in modern Catalysis. Photoorganocatalysis, the use of small organic molecules for photocatalytic transformations, has provided new chemical reactivities and synthetic pathways through the mild generation of radical species. In our laboratory, we have developed several methods that harness the power of light through the use of small organicphotocatalysts. Oxidation of alcohols is one of the most important reactions in Organic Chemistry and Chemical Industry. Herein, we report a cheap, green and metal-free photochemical protocol for the oxidation of alcohols, utilizing air as the oxidant. A variety of substituted benzylic and secondary alcohols have been converted into the desired carbonyl compounds, in moderate to high yields. Extended and detailed mechanistic studies have been conducted, in order to determine the plausible mechanism of the reaction.



PRODRUGS OF 6-DIAZO-5-OXO-L-NORLEUCINE: STRATEGY FOR DELIVERY IN BRAIN AND POTENTIAL TREATMENT OF LYMPHOMA

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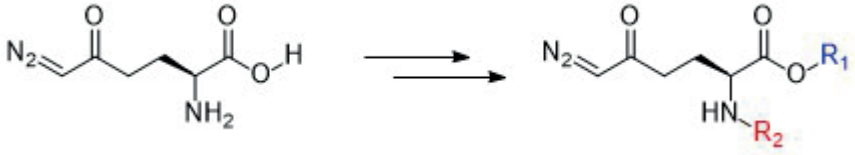
6-diazo-5-oxo-L-norleucine (DON), a non-natural amino acid with structural similarity to glutamine, was first isolated from Streptomyces bacteria in the 1950s. It has shown promissing antitumor activity in preclinical and several clinical studies. DON acts as an irreversible inhibitor of many glutamine utilizing enzymes critical for the synthesis of nucleic acids, proteins and the generation of α-ketoglutarate for energy metabolism. However, its high toxicity leading to gastrointestinal side effects prevented its further development. We hypothesized that a novel cell-directed prodrug of DON which could deliver the drug selectively to cells and would permit significant dose reduction, greatly alleviating the GI adverse events.



Herein we report the design, synthesis, and evaluation of several novel DON prodrugs targeted to Peripheral Blood Mononuclear Cells (PBMC's). Using whole blood from mouse, pig, dog, monkey and human, we found that several of the new prodrugs selectively delivered DON into PBMC's versus plasma by >10-fold. These findings open an opportunity to develop therapeutics active at lower dose circumventing dose limiting toxicities.

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MULTITARGET TRIAZOLES: AN INNOVATIVE APPROACH FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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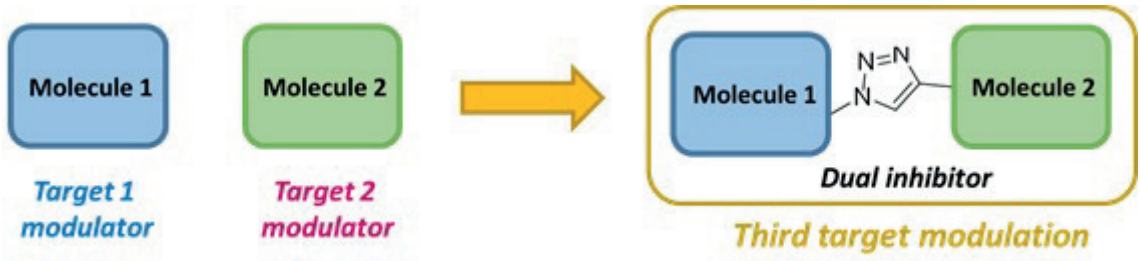
Multitarget drugs are molecular entities that are designed to present more than one biological activity. They are arising as powerful tools to tackle complex diseases including bacterial resistances, cancer or neurodegenerative diseases. Typically, the rational strategies to design multitarget drugs are linkage, fusion and incorporation or merge. Here we present the creation of a multitarget drug combining active fragments in a way that could inhibit an additional third target with the objective to create powerful modulating agents for neurodegenerative diseases. Multitarget compounds are ideally suited for the treatment of these pathologies due to their unknown etiology, multifactorial pathology and lack of efficient treatments. To achieve this aim we have combined fragments that inhibit kinases involved in the main pathomolecular pathways of Alzheimer's disease such as tau aggregation, neuroinflammation and decreased neurogenesis, looking for a third action in BACE1, responsible of β-amyloid production. To synthesize the multitarget compounds we have employed the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC)[1,2] methodology to obtain the 1,4-disubstituted triazoles. The synthesized triazoles exhibited three inhibitory activities against the desired targets.
Finally, and after the successful results obtained using this methodology, we have started to implement the in situ click chemistry technique[3] to better select the multitarget compounds using BACE1 as a template.



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MOLECULAR REQUIREMENTS FOR THE EXPRESSION OF ANTIPLATELET EFFECTS BY SYNTHETIC STRUCTURAL OPTIMIZED ANALOGUES OF THE TYROSINE KINASE'S INHIBITORS, IMATINIB AND NILOTINIB

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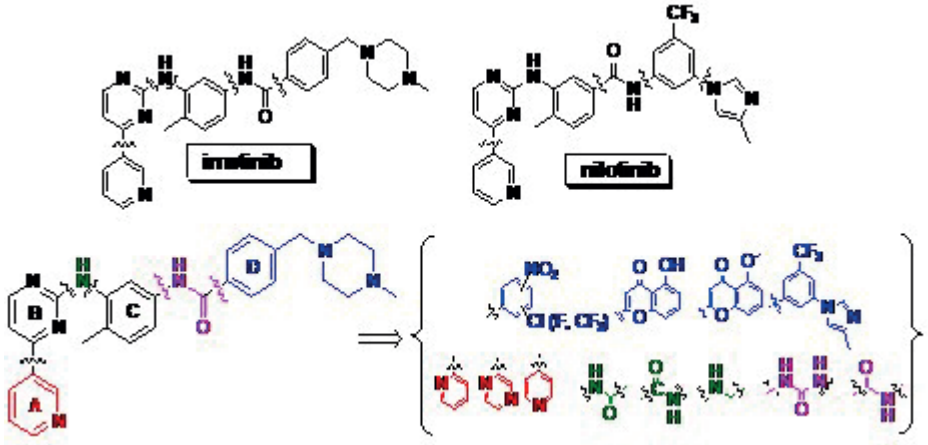
The objective of this study is the design and synthesis of analogues of the TKIs imatinib and nilotinib in order to develop tyrosine kinase inhibitors, by investigating their molecular requirements, which would express antiplatelet and therefore antithrombotic properties. hrombosis is a leading direct cause of morbidity, mortality, and cost of care in cancer patients. The pathogenesis of thrombosis in cancer is multifactorial, including various platelet alterations. Tyrosine kinases play important roles in tumor biology, thus tyrosine kinase inhibitors (TKIs) represent the most important class of anticancer drugs, based on the concept of targeted therapy. In Particular, protein kinases are enzymes that play pivotal role in cell functions regulating many signal pathways by inducing ATP phosphorylation. Dysregulation of protein kinase and their receptors activity has been related to various diseases, including chronic myeoid leukemia and atherosclerosis. Inhibition of these pathological protein kinases through small molecular weight compounds that compete the ATP binding site in the kinase active core is found to contribute in the treatment of the disease symptoms. For this reason, there is great interest in the scientific community for the synthesis and development of new more potent protein kinase inhibitors, acting selectively in the pathological protein kinase. Imatinib (Gleevec) is the first selective inhibitor who antagonizes the ATP binding site in the pathological Bcr-Abl tyrosine kinase in the treatment against chronic myeloid leukemia (CML), while recent clinic results show its atheroprotective role. Nilotinib was designed as a second generation selective Bcr-Abl kinase inhibitor and exhibits greater inhibitory activity compared to Imatinib.Bearing in mind the biological results demonstrated by the previous synthetic analogues of the pharmaceutical preparation of Imatinib in cooperation with the Novartis Institute for Biomedical Research and the Imperial College of London, Faculty of Medicine, we look forward to the development of new, more active and selective inhibitors. The biological control of the inhibitory effect of a sufficient number of new compounds, analogs of the pharmaceutical formulation Imatinib (Glivec), against a large number of protein kinases, such as B-Raf, PKA, Abl, CDK2 / A, c-Src, IGF-1R ., demonstrated in some cases strong inhibitory and selective activity at sufficiently low concentrations (IC50: ~ 15-100 nM). New compounds, Nilotinib analogues/derivatives, were synthesized in the laboratory, as a result of molecular modeling and it is possible to act more effectively on the protein kinases targets, aiming at their selective inhibition. These modifications on the original pharmaceutical compounds were targeted and were about the pyrimidine and the last phenyl ring, where groups that increase the hydrogen bonds and the aromatic ability were added (table 1). All new compounds were fully characterized (^{1}H NMR, ^{13}C NMR, IR, MS).



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SYNTHESIS OF N-PHENYLBENZAMIDE-BASED COMPOUNDS AS CHEMOTHERAPEUTIC AGENTS AGAINST KINETOPLASTID PARASITES

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Diseases caused by protozoan parasites are particularly devastating and are a cause of great morbidity and mortality in the developing world. Parasitic diseases caused by kinetoplastid endoparasites such as *Trypanosoma cruzi* (Chagas disease) or *Leishmania* (leishmaniasis) are particularly neglected and these remain a major source of poverty in developing countries.

The drug currently used to treat Chagas disease and leishmaniasis are decades old and have many limitations, including severe side-effects, and low to medium efficacy and selectivity. In addition, the increasing multi-drug resistance of pathogenic parasites to therapeutic agents (e.g. antimonial drugs) requires the development of new compounds that are safe, effective and less vulnerable to the development of drug resistance.

Kinetoplastid parasites present remarkable features, such as a single mitochondrion that contains an enlarged region, termed kinetoplast, which harbours the mitochondrial DNA (kDNA). Recent examples in the literature have shown that AT-specific minor groove binders that disrupt DNA-protein interactions involved in the replication and repair machineries are an effective strategy to kill kinetoplastid parasites.[1-4]

In this project, we synthesized several families of heterocylic compounds based on the *N*-phenylbenzamide scaffold as potential kDNA binders that can be useful chemotherapeutic agents against *Leishmania* and *T. cruzi* parasites.

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ELECTROCHEMICAL TRYPTOPHAN-SELECTIVE BIOCONJUGATION

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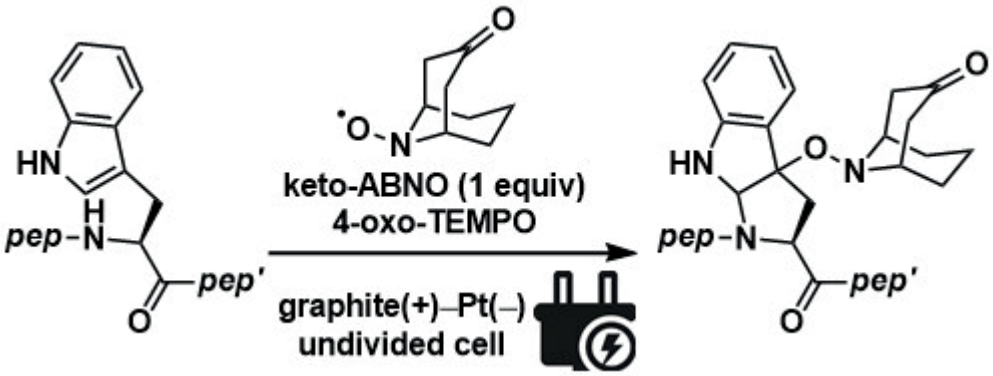
A bioconjugation reaction targeting proteinogenic amino acids is an attractive methodology providing new drugs and diagnostic methods by enabling functional expansion of proteins. In 2016, our group reported metal-free, tryptophan-selective protein bioconjugation in water, using the sterically less-hindered organoradical (ABNO derivatives) as the reactant [1]. However, relying on the acidic conditions (pH 3~4) and nitrogen oxides activator may hamper the general utility by causing protein aggregation and side reactions.

To improve these points, we attempted electrochemical activation of the ABNO derivatives in neutral media. When constant-voltage electrolysis is applied to the solution of tryptophan-containing peptides and keto-ABNO, an expected bioconjugate was obtained. The reaction proceeded more efficiently by adding structurally distinct organoradical (4-oxo-TEMPO), which is inert to tryptophans. The reaction could also be applied to water-soluble peptide/protein. This is the first example of tryptophan-selective electrochemical protein bioconjugation[2]. Cyclic voltammetry (CV) analysis suggested that the bioconjugation proceeded through an intermediate of interacted tryptophan and keto-ABNO. CV study also suggested that 4-oxo-TEMPO can act as an electrochemical mediator for this oxidative bioconjugation.



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BIOLOGICAL EVALUATION OF NEW ANTHRAQUINONE DERIVATIVES AS ANTI-CANCER AGENTS

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Cancer is a group of diseases involving abnormal cell growth occurring in every population and with a relatively high mortality rate. In developed countries, this is the second cause of death, after cardiovascular diseases. According to WHO data from 2018, the most common cause of death from cancer is lung cancer (1.76 milions death). Anthraquinones is a group of compounds commonly found in nature. They are derivatives of anthracene with interesting chemical properties. Some of the anthraquinone derivatives also have biological activity. Many compounds in this class are active and commonly used in cancer chemotherapy (doxorubicin, daunorubicin, mitoxantrone and others) (1).

The aim of the study was to evaluate mechanism of action responsible for cytotoxic properties of novel derivatives of anthratriazinones, which can be regarded as derivatives of antraquinone. These compounds possess good cytotoxic properties against A549 cells (human non-small cell lung cancer) with IC_{50} in micromolar range (1-7.5).We found, that investigated compounds are potent inducers of DNA double strand breaks. Intracellular γ-H2AX immunostaining reveal strong increasment of histon focie formation after drug treatment and this is at least partially associated with inhibition of DNA topoisomerase II alpha. The presented studies exhibit that newly synthesized antratriazinones show promising antitumor properties.

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DIELS-ALDER ADDUCTS OF OLIGOMYCIN A: SYNTHESIS AND BIOLOGICAL ACTIVITY

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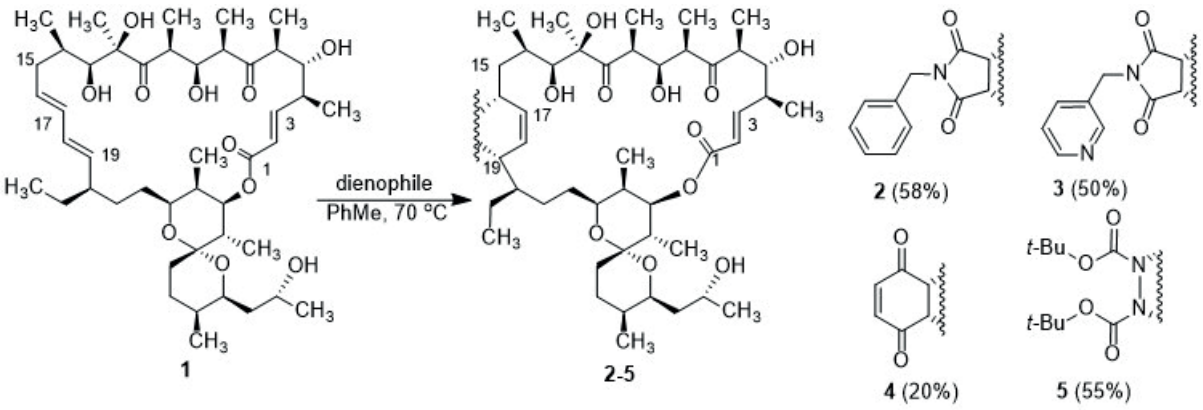
Natural compounds have been considered in drug discovery as “privileged structures” due to their high affinity to biomolecules which were evolutionarily selected by the nature. Oligomycin A (**1**) inhibit F_1Fo ATP-synthase, which is regarded as a molecular target for new drugs in the treatment of tumors and infections. However, high toxicity of oligomycin A for mammalian cells confines its clinical application. So, a chemical modification of oligomycin A is one of the possible ways to improve its pharmacological properties.

Cycloaddition reactions are widely spread in medicinal chemistry as a powerful tool for the synthesis and functionalization of diene-containing bioactive compounds [**1**]. The structure of oligomycin A (**1**) represents a 26-membered lactone core with a conjugated diene, fused to a spiroketal moiety, containing a hydroxypropyl side chain. The (E,E)-configuration of the C16-C19 diene system allows for oligomycin A to react with active dienophiles in Diels-Alder (DA) reactions. Cycloaddition of N-benzylmaleimide, N-(3-picolyl)maleimide, benzoquinone and di(*tert*-butyl)azodicarboxylate to oligomycin A (**1**) in toluene at 70 ^{O}C proceeded with moderate selectivity, resulted in preferably *cis*-endo adducts **2**-**5**. The ratio of cis-endo isomers **2** and **3** to corresponding side *cis*-exo-isomers is approximately 2.5:1. Exo-isomers of products **4** and **5** were not isolated due to small amounts of their formation.



Structures of compounds **2**-**5** were confirmed by high-resolution mass spectrometry and NMR spectroscopy, including 2D experiments. Relative configurations of C16 and C19 positions were determined by the analysis of correlations in ^{1}H-^{1}H ROESY spectrum.

DA-type modifications of the oligomycin A structure negatively affected on the antifungal activity: compounds **2**-**5** were in 100-1000 times less active against *Candida* strains and filamentous fungi in comparison with the parent antibiotic **1**. However, sensitivity of the leukemia cell line K-562 to derivatives **2**-**5** retained on the same level as for oligomycin A. In-depth evaluation of biological properties of DA-adducts of oligomycin A **2**-**5** is ongoing now.

This work was supported in part by Russian Science Foundation (grant 15-15-00141).

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MINIFRAGS - CRYSTALLOGRAPHIC SCREENING USING ULTRA-LOW MOLECULAR WEIGHT LIGANDS TO GUIDE DRUG DESIGN

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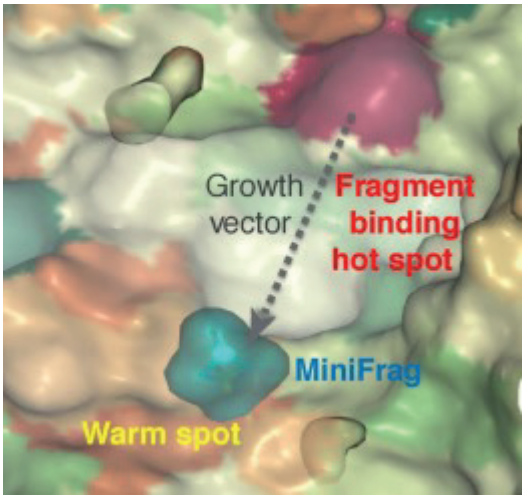
High throughput crystallographic fragment screening is core to Astex's technology and routinely identifies fragment 'hits' (heavy atom count < 12) binding at a diversity of sites, or 'hot spots' on a target protein. As a complementary methodology to traditional fragment X-ray screening the 'MiniFrags' technology has been recently developed at Astex.[1]

MiniFrags is a novel crystallographic screening methodology that employs high concentration aqueous soaks with a chemically diverse and ultra-low-molecular-weight library (HAC 5–7) to identify ligand-binding hot and warm spots on proteins. We propose that MiniFrags, used in concert with Fragment screening, represents a broadly applicable and powerful tool for identifying energetically favourable interaction points on proteins. This methodology provides a highly effective technique for guiding optimisation of fragment-derived lead compounds or chemical tools and that the high screening hit rates reflect enhanced sampling of chemical space. We have successfully screened the Minifrags library against several targets, which will be exemplified using ERK2 as a case study.



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3D PHARMACOPHORE-BASED VIRTUAL SCREENING FOR NOVEL CHYMASE INHIBITORS BY IN SILICO FRAGMENT MAPPING

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The term chymase refers to a family of chymotrypsin-like serine proteases stored within the secretory granules of mast cells. Recently, a variety of small molecule inhibitors for chymase have been developed with a primary focus on the treatment of cardiovascular diseases. Despite the expected therapeutic benefit of these chymase inhibitors, they have not been used clinically. Here, we attempted to identify new chymase inhibitors using a multistep structure-based virtual screening protocol combined with our knowledge-based *in silico* fragment mapping technique.

The screening procedure makes the most of a database named as the Canonical Subsite-Fragment DataBase (CSFDB) and the knowledge-based fragment mapping program Fsubsite. The CSFDB consists of various pairs of subsite-fragments derived from X-ray crystal structures of known protein-ligand complexes. Fsubsite searches the surface of a target protein for similar topographies to subsites stored in the CSFDB. When a local topography similar to the subsite is found on the target protein, Fsubsite places the corresponding fragment with its matching subsite. In this study, the mapping procedure identified fragments with novel modes of interaction at the oxyanion hole of chymase. Next, we constructed a three-dimensional (3D) pharmacophore model and retrieved eight candidate chymase inhibitors from a commercial database that included approximately five million compounds. This selection was achieved using a multistep virtual screening protocol, which combined a 3D pharmacophore-based search, docking calculations, and analyses of binding free energy. One of the eight compounds exhibited concentration-dependent chymase inhibitory activity, which could be further optimized to develop more potent chymase inhibitors.

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NEW IMIDAZOPYRIDINE NUCLEOSIDE DERIVATIVES AND EVALUATION OF THEIR ANTIVIRAL ACTIVITY

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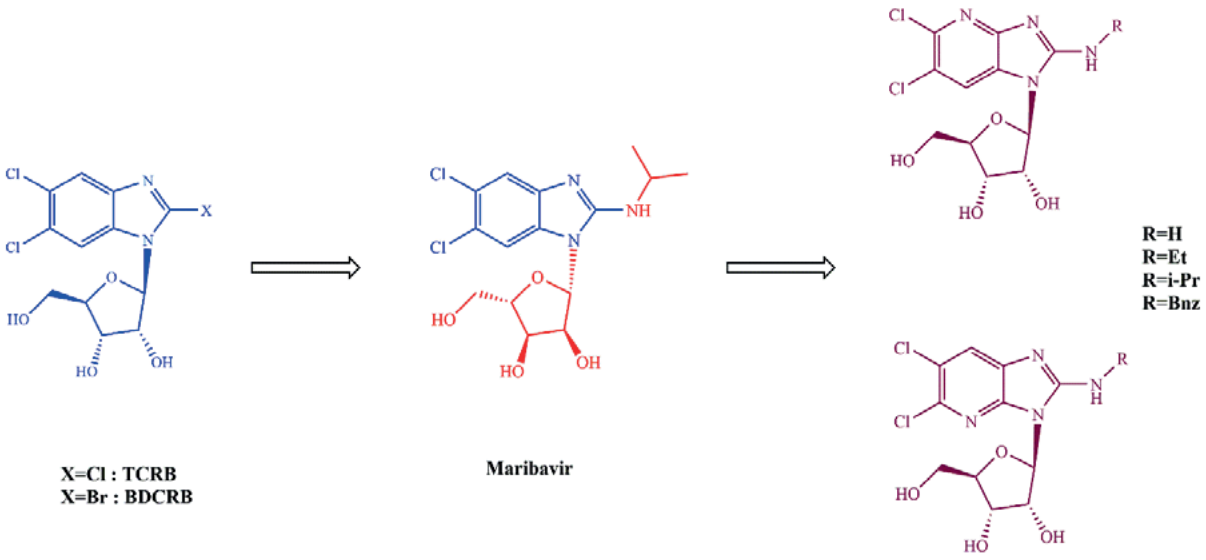
Human Cytomegalovirus (HCMV) is the most common sight- and life-threatening opportunistic pathogen in immunocompromised individuals[1]. Ganciclovir is still the gold standard for the treatment of HCMV infectious manifestations, while Cidofovir and Foscarnet serve as second-line therapies. However, the clinical effectiveness of these compounds is limited[2] and the recent approval of the terminase inhibitor Letermovir with fast-track procedures[3] highlights the urgent need for anti-HCMV agents with novel modes of action and improved clinical safety. In this scope, research efforts led to the development of polyhalogenated benzimidazole nucleosides, exemplified by 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole (TCRB) and its 2-bromo analogue (BDCRB), that were found to strongly inhibit viral replication[4]. The 2-isopropylamine substituted derivative of the β-L-series Maribavir has proven to be more potent than BDCRB, reducing HCMV DNA synthesis via the inhibition of the viral kinase UL97 and has entered clinical trials[5].



In order to expand the structure-activity relationships of the benzimidazole series to the less studied and more "purine-like" imidazo[4,5-*b*]pyridine scaffold, we have developed a number of novel nucleoside derivatives, which can be considered as 4-aza-D-isosters of Maribavir. Our aim is to explore the spatial limitations of the target enzymes and gain insight on the network of interactions developed. Within this context, we disclose herein the preparation and pharmacological evaluation of the 1- and 3-regioisomeric β-D-ribosides of 5,6-dichloroimidazo[4,5-*b*]pyridine, introducing various aminosubstituents at the vacant position of the imidazole ring.

**This work has been carried out in the framework of the author's M.Sc. Scholarship granted by the Onassis Foundation*

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DESIGN AND SYNTHESIS OF NON-NUCLEOSIDE DERIVATIVES OF IMIDAZO[4,5-b]PYRIDINE AND EVALUATION OF THEIR ACTIVITY AGAINST HEPATITIS B VIRUS

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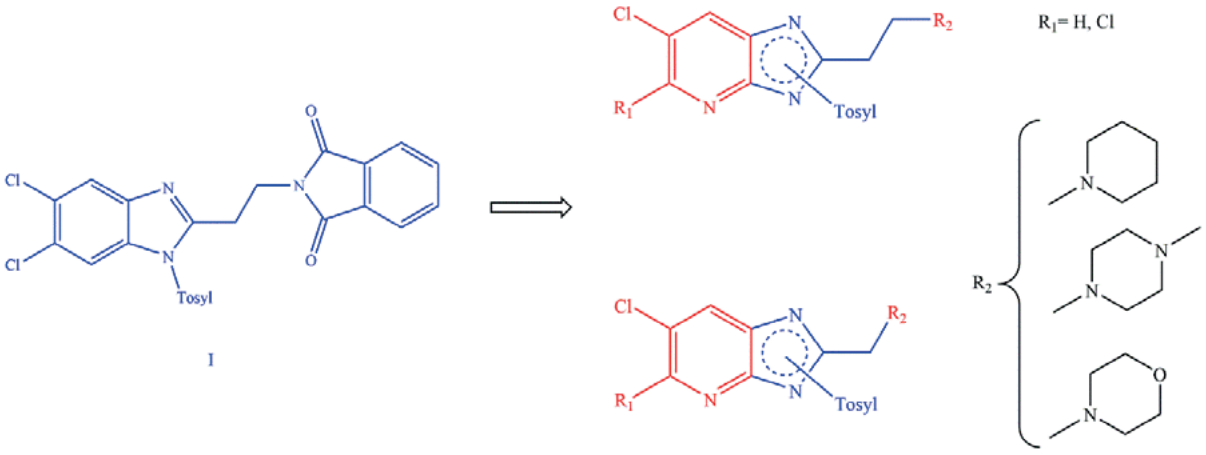
Hepatitis B virus (HBV) infection is a world leading cause of chronic liver disease. The employment of vaccination strategies has not resulted in eradication of the virus and infection still poses serious health problems, especially in developing countries[1]. Consequently, pharmacological intervention is an effective way to reduce mortality from cirrhosis and hepatocellular carcinoma. Two major classes of antiviral agents are utilized in chronic hepatitis B, namely interferons and nucleos(t)ide derivatives. However, severe side effects related to interferon treatment[2] and the high emergence of HBV drug-resistant strains underline the clinical need for novel classes of compounds[3]. Within this context, the development of non-nucleoside benzimidazole inhibitors of HBV provides a promising therapeutic strategy. Among them, compound I exhibited high antiviral potency and selectivity index[4].



In an effort to contribute to the structure-activity relationship studies of these series we have prepared a number of novel compounds possessing the imidazo[4,5-*b*]pyridine scaffold and investigated their biological activity as potential HBV inhibitors. The new compounds bear different substitution patterns on the fused pyridine ring, while the phthalimide moiety has been replaced by alicyclic amines. Furthermore, in order to identify the optimal chain length between the imidazopyridine core and the amino group, different alkyl linkers have been introduced. Target compounds are also considered the corresponding tosyl derivatives, which have been prepared from the tosylation of the heterocyclic bases, leading to both 1- and 3-regioisomers of imidazo[4,5-*b*] pyridine.

**This work has been carried out in the framework of the author's M.Sc. scholarship granted by the Onassis Foundation*

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SYNTHESIS AND BIOLOGICAL EVALUATION OF RHENIUM TRICARBONYL ENROFLOXACIN AND LEVOFLOXACIN COMPLEXES

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Organometallic rhenium complexes have been evaluated as novel antiproliferative agents in recent studies. A series of “2+1” mixed ligand rhenium(I) tricarbonyl complexes was synthesized with the quinolone antimicrobial agents enrofloxacin (Herx) and levofloxacin (Hlfx) and methanol, imidazole (im) or pyridine (py) as co-ligands. The complexes were characterized by spectroscopic methods. The interaction of the rhenium complexes with bovine serum albumin was investigated by fluorescence emission spectroscopy and the corresponding binding constants were determined. The binding of the rhenium complexes to calf-thymus DNA (CT DNA) was monitored by UV-vis spectroscopy, viscosity measurements and competitive studies with ethidium bromide (EB). These studies indicated that intercalation is the most possible mode of action and the corresponding DNA-binding constants of the complexes were calculated. The toxicity of the Re-complexes was evaluated in human K–562 erythroleukemia cells over 48 h in varying concentrations. From this series, [$Re(CO)_3$(erx)(im)] was identified as the most potent cytotoxic agent against K-562 cells. These preliminary results are promising and warrant the design of new Re-complexes with improved properties in future studies.

SYNTHESIS OF RHENIUM TRICARBONYL COMPLEXES WITH FLAVONOIDS AND EVALUATION OF THEIR ANTIOXIDANT PROPERTIES

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Flavonoids are natural polyphenols many of which have potent antioxidant activity and they have been evaluated in several pathological disorders, including Alzheimer's disease, cardiovascular disease, inflammation and cancer. This study aims in the synthesis and initial biological evaluation of novel rhenium tricarbonyl complexes of the flavones 3,7,4′-trihydroxyflavone (resokaempferol), 3-hydroxyflavonol (flavonol), 5,7-dihydroxyflavone (chrysin) and 4′,5,7-trihydroxyflavonone (naringenin). Resokaempferol and flavonol were synthesized from the corresponding chalcones, 2,2′,4-trihydroxychalcone and 2′-hydroxychalcone, by using H_2O_2 in a NaOH solution. The preparation of 2′-hydroxychalcone was carried out via Claisen-Schmidt condensation. The rhenium-tricarbonyl complexes of the type *fac*-[$Re(CO)_3(FL)(CH_3OH)$] were synthesized by reacting the precursor *fac*-[$Re(CO)_3(CH_3OH)_3]^+$ with an equimolar amount of the above mentioned flavones (FL), where FL is resokaempferol, flavonol, chrysin and naringenin. The respective Re-flavone complexes were purified by semi-preparative HPLC and then characterized by spectroscopic methods. The stability of the Re-complexes in DMSO solutions was high. The Re-flavone complexes were assessed *in vitro* for their antioxidant properties by the DPPH assay as well as for their ability to inhibit peroxidation of linoleic acid in the presence of AAPH and to inhibit *in vitro* soybean lipoxygenase (LOX). All the Re-complexes interact with the free stable radical DPPH exhibiting increased reducing abilities compared to the respective free flavones, which increased over time. The Re-chrysin and Re-naringenin present moderately higher inhibition of LOX compared to the free flavones, while significant decrease in LOX inhibition was observed by Re-resokaempferol and Re-flavonol compared to the respective free flavones. Given the fact that Re-tricarbonyl complexes recently attract attention due to their promising pharmaceutical and biological properties as well as their application in the development of analogous ^{99m}Tc-radiopharmaceuticals, this preliminary study of the antioxidant and inhibitory properties of these Re-flavone complexes is of significant interest, while further evaluation of their biological properties will be in progress in the future.

SYNTHESIS AND BIOLOGICAL EVALUATION OF CINNAMIC ACID DERIVATIVES DESIGNED AS AGENTS AGAINST NEURODEGENERATION

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Neurodegenerative disorders include a range of conditions, characterized by the progressive loss of neuronal function. Due to their multifactorial nature, therapeutic strategies against neurodegenerative disorders are ineffective until now. As a result, these conditions pose a significant socioeconomic burden to society.

Alzheimer's Disease (AD) is one of the most common neurodegenerative disorders, that affects an increasing amount of population, as life expectancy rises. Therapeutic agents against AD include Acetylcholinesterase Inhibitors, which have only symptomatic efficacy, but they do not contribute to the radical treatment of the disease. Recent therapeutic strategies suggest the design of molecules, which combine two or more pharmacophores and thus affect various targets, associated with the pathology of such diseases. Oxidative stress and inflammation have been found to play a key role in the progression of AD. Lipoxygenase overexpression is responsible for neuronal vulnerability. Moreover, oxidative damage in lipids, proteins and nucleic acids is critical to the etiology of neurodegeneration.

In this work some cinnamic acid derivatives with antioxidant properties, such as ferulic and sinapic acid, were amidated or esterified with compounds, which are expected to act in the Central Nervous System. Proline is the main pharmacophore of nootropic agents (piracetam, aniracetam), while GABA is the main inhibitory neurotransmitter in brain. GABAergic abnormalities may contribute to AD progression. Gabapentin is a neuroprotective agent used in treatment of epilepsies and Nipecotic acid has been found to inhibit GABA reuptake in GABA receptors. Finally, cinnamyl alcohol has been found to increase LOX inhibitory activity of anti-inflammatory agents and some thiomorpholine derivatives offer anti-hyperlipidemic activity to compounds.

The synthesized compounds were found to have in vitro anti-oxidant activity, to exert anti-inflammatory activity, assessed as paw edema reduction and to inhibit lipoxygenase activity. In addition, some of them possess significant AchE inhibitory activity, while others decrease cholesterol and triglyceride levels in hyperlipidemic rats.

With the design of the described derivatives we aimed to compounds that would acquire a series of biological properties able to prevent or restore several pathological changes implicated in AD and appearing in the demented brain. This study has demonstrated that, in general, the synthesized compounds possess a combination of the desired properties integrated in their molecules. Some Structure-Activity Relationships (SAR) have also been reached.

G. Papagiouvannis acknowledges the General Secretariat for Research and Technology (GSRT) of Greece and the Hellenic Foundation for Research and Innovation (HFRI) for a grant supporting his PhD research

NEW ANTITUBERCULAR ISONIAZID-ADAMANTANE HYDRAZONE DERIVATIVES: DESIGN, SYNTHESIS, EVALUATION, COMPUTATIONAL STUDIES AND IN VITRO CONTROLLED RELEASE STUDIES

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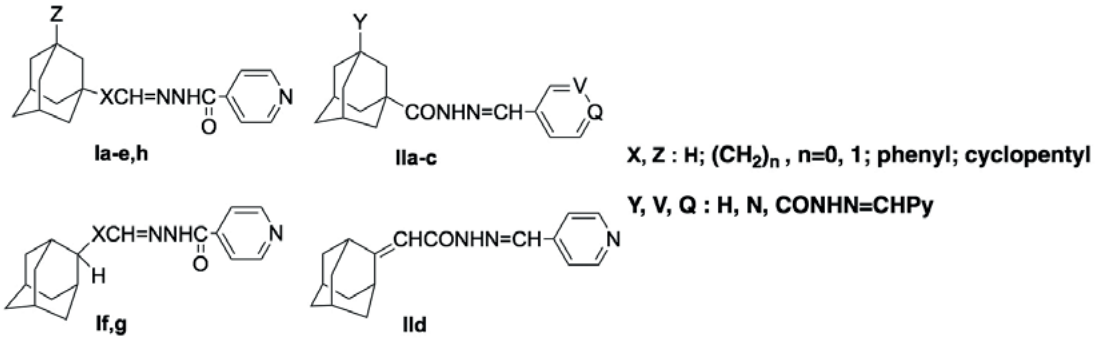

Alongside HIV/AIDS and malaria, tuberculosis (TB) is one of the three major microbial lethal threats to human history in developing and industrialized countries worldwide. Besides the gravity of the disease, TB receives insufficient funding and research on new drugs is less intense compared to other diseases. The emergence of drug-resistant strains of *Mycobacterium tuberculosis*(Mtb) has led to attempts to develop new drugs that are more efficient than today's regimen.

Various adamantane derivatives with promising antitubercular potency, have recently been developed. Our laboratory exploiting our experience on adamantane derivatives, has recently reported the synthesis and biology of a series of antimycobacterial adamantane adducts.[1-4]In our ongoing search for new potent compounds, the design and synthesis of twelve new isoniazid-based adamantane derivatives (compounds **I**and **II**, Figure) is presented herein. Amongst its congeners, the adamantane isocotinoyl hydrazone **Ia** exhibits the best antitubercularactivity (MIC=0.04 μg/mL) and the lowest cytotoxicity (SI=2500). The pharmacological test results and the dissolution profile, in aqueous gastrointestinal simulated media, of representative examples of the new molecules were found to be in agreement with the computational results obtained from docking poses and molecular dynamics simulations on the tested compounds.

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TOWARDS THE DEVELOPMENT OF NOVEL ANTI-HBV AGENTS: BLOCKAGE OF VIRUS REPLICATION BY N-HYDROXYIMIDES THROUGH INHIBITION OF RIBONUCLEASE H

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Hepatitis B Virus (HBV) is a DNA virus in the *Hepadnaviridae* family. Long-term HBV infections constitute a major cause of end-stage liver disease and chronic carriers are at risk of developing cirrhosis, liver failure and hepatocellular carcinoma. Current antiviral therapy (immunomodulators, nucleos(t)ide analogues) rarely eradicates the virus and apparently cleared HBV infections can be reactivated during immunosuppression. Moreover, HBV's high mutation rate can lead to drug resistance. To cure HBV infection, it is crucial to develop new strategies, including achieving profound viral suppression.

HBV Ribonuclease (RNaseH) is a metalloenzyme that belongs to the nucleotidyl transferase superfamily and its active site contains four carboxylates that bind to two Mg^{2+} ions required for the RNA cleavage. However, the potential of RNaseH as a drug target for HBV treatment, was never seriously explored until recently. The importance of the RNaseH, along with the fact that there is no discernable amino acid homology between the HBV enzyme and the cellular RNaseHs, prompted the development of novel scaffolds, bearing a metal-chelating motif, as potent inhibitors.[1]

Utilizing findings in the literature and our previous publications,[2] we have rationally designed and synthesized a series of metal chelating agents (*N*-hydroxyimides) to optimize our lead compound. The novel analogues were tested for their anti-HBV activity, and they were considerably potent with EC_{50} values in the mid nM range. Our studies indicate that this class of compounds holds significant potential for antiviral development. Our future studies will be informed by our growing structure activity relationships.

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3-FLAVONOLS AND RELATED ESTERS/CARBAMATES AS NOVEL QUORUM SENSING INHIBITORS

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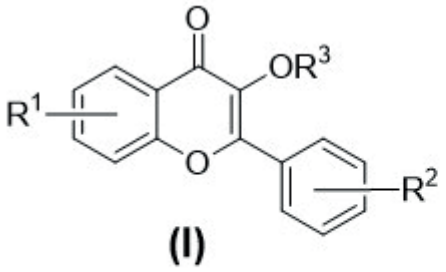
Biofilm formations are the major cause of chronic infections and nosocomial infections all over the world due to their inherent tolerance and 'resistance' to antimicrobial treatments.[1] However, no specific anti-biofilm drug is available in the market to date. Gram-negative bacteria, such as *Pseudomonas aeruginosa*, is the main cause of mortality in patients with cystic fibrosis and urinary tract infections.[2] Since bacterial cell-to-cell communication network, termed as quorum sensing (QS), plays a major role in biofilm formation as well as virulence and pathogenicity, targeting QS offers a unique opportunity to tackle such bacteria.[3,4] Importantly, QS does not affect the bacterial growth, hence, QS inhibitors (QSIs) are less prone to resistance and can enhance antibiotics' efficacy. By means of *in vitro* assays, our colleagues have recently reported the identification of flavonoid analogues capable of interfering with the LuxI/LuxR QS system of Gram-negative bacterium *P. aeruginosa* at micromolar levels. Moreover, these hits have affected some important QS-mediated functions in Gram-negative species, such as the inhibition of biofilm lifecycle at different stages. Hence, these hits hold the potential for further development to inhibit or eradicate biofilm. Herein, we present our recent findings related to structure-activity relationships (SARs) of flavonols and related esters/carbamates (Fig. 1) as QSIs and provide insight into key structural features required to maintain anti-*quorum* sensing activity.[5,6]



(I)

R^1 & R^2 = -H, -Cl, -Br, -OBn, -OH, -OMe, etc.

R^3 = -H, $-(CH_2)_nCH_3$ (n=0,1,2,3,etc.), $-CONH(CH_2)_nCH_3$ (n=0,1,2,3,etc.)

Fig. 1. General structure of flavonols and related esters/carbamates.

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ANTIMYCOBACTERIAL ACTIVITY OF HARMINICES, HARMINE AND CINNAMIC ACID HYBRIDS

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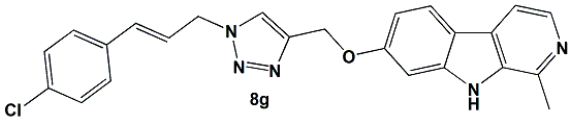
Tuberculosis (TB) remains one of the major global health problems with 10 million new cases (1 million children) annually. In 2017 TB was one of the top 10 causes of death worldwide killing 1.3 million people, ranking above HIV/AIDS as the leading cause of death from an infectious disease (1).

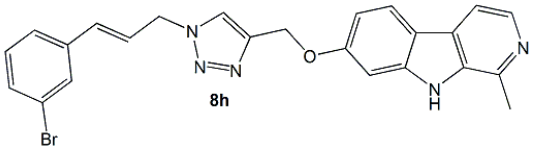
New treatment options are urgent in order to resolve some of the major issues in current anti-TB therapy; the emergence of multidrug-resistant (MDR-TB) and extensively drug resistant (XDR-TB) strains which require prolonged and complex treatment, as well as toxicity. In the las decade, the efforts in antimycobacterial drug discovery resulted in two new oral drugs for the treatment of TB, delamanid and bedaquiline (2).

Harmine, an alkaloid of the β-carboline type, and its numerous derivatives exert a broad spectrum of pharmacological activities. Antimycobacterial screening was performed as well and it has shown some promising results (3-5). Cinnamic acid and its derivatives are naturally occurring substances found in various plants, and possess diverse pharmacological activities.

Such findings prompted us to evaluate antimycobacterial activity of harmicines, hybrids of harmine and cinnamic acid derivatives. Minimum inhibitory concentrations (MIC) were determined in *Mycobacterium tuberculosis* H37Rv, a virulent strain, by using the resazurin reduction microplate assay. Compounds **8g** and **8h** inhibited the growth of the *M. tuberculosis* H37Rv, with MIC values of 10 μM, while isoniazid MIC was 1.25 μM. Further evaluations are necessary to investigate the toxicological properties, as well as the potential of **8g** and **8h** as new anti-TB drug candidates.



8g



8h

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CROP PROTECTION - SYNTHETIC CHALLENGES AND METHODOLOGIES

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ASCENZA is an international crop protection company with the mission “Feed the planet, through healthy and safe solutions, enabling a balanced and sustainable agriculture".

The registration process for plant protection products involves performing of numerous studies to prove the safety of the product both for the environment and for humans (both consumers and applicators) as well as its efficacy. In order to make this possible, active ingredient synthesis strategies (in industrial scale) may have to be developed, impurities in technical grade active ingredient samples have to be identified and synthesized (or isolated) and metabolites have to be synthesized ranging from hundreds of milligrams (analytical standards) to tens of gram (test items for toxicity or ecotoxicity evaluation). Research and Development of new strategies for the synthesis and purification of pharmaceutical and phytopharmaceutical active ingredients, metabolites and impurities have been one of the main goals of Industry and Academy. ASCENZA is driven by this goal to pursue new, more efficient and more sustainable methodologies and technologies.

Our team is focused in the synthesis of metabolites, impurities and its purification and isolation from active ingredients.

This communication will show part of the work developed in ASCENZA's laboratory facilities based in Setúbal.

VISIBLE LIGHT-MEDIATED SYNTHESIS OF γ-CYCLOBUTANE AMINO ACIDS AND THEIR APPLICATION AS BUILDING BLOCKS FOR BIOACTIVE PEPTIDES

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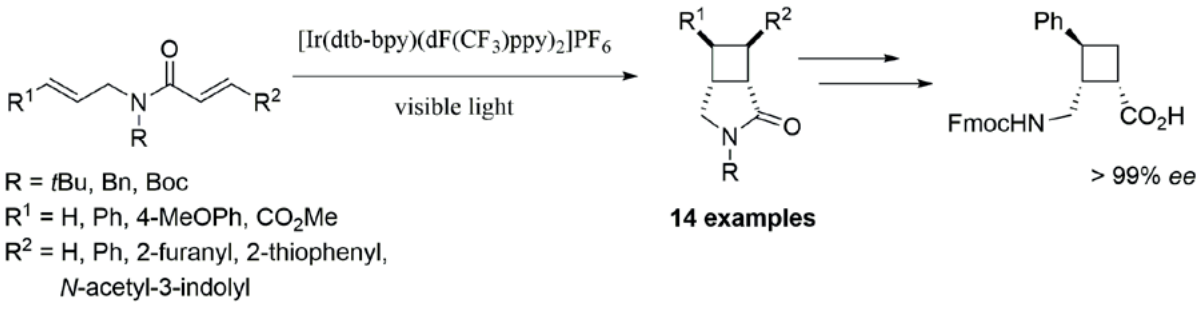
Combining unnatural cyclic amino acid residues and natural α-amino acid residues in a single chain affords oligomers with useful properties, such as stabilized secondary structure and stability against enzymatic degradation. Thus, cyclic amino acids as building blocks for relevant peptides have emerged as promising compounds in medicinal chemistry.

We investigated the synthesis of γ-cyclobutane amino acids with an intramolecular visible light-mediated [2+2]-cycloaddition as the key step. Starting with amide-linked dienes, cycloaddition proceeds through energy transfer mechanism and furnishes corresponding bicyclic compounds in good yields and with excellent diastereoselectivity. After the transformation of the obtained bicyclic compounds into racemic *N*-Boc-*cis* -γ-cyclobutane amino acids and the chiral resolution of latter, enantiomerically pure corresponding amino acids were prepared.



To develop new selective ligands for neuropeptide Y (NPY) receptor subtypes, NPY native α-amino acid residues were replaced with the newly synthesized *N*-Fmoc-*cis*-γ-cyclobutane amino acids to afford truncated NPY analogues.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW ARTEMISININ-STEROID HYBRID MOLECULES

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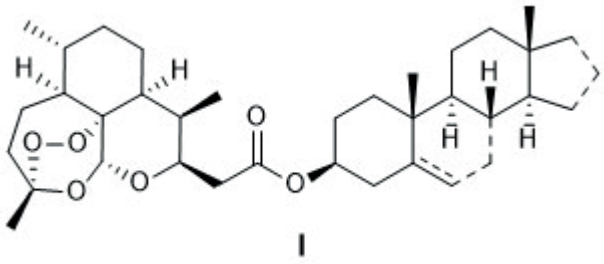
Natural 1,2,4-trioxane sesquiterpene artemisinin and its bioactive semi-synthetic derivatives, such as dihydroartemisinin, artesunate and artemether, have been proved a milestone in the treatment of malaria[1], including multidrug resistant strains of the disease.[2] Besides the antimalarial effects, artemisinins exhibit a broad range of biological activities, such as interesting antitumor properties.[3,4] Nevertheless, in recent days, due to global warming and consequential growth of resistant malaria parasites to ART-based drugs in some regions of the world, the WHO has recommended ART-based combination therapies (ACTs).[5,6] In an effort to develop more effective antimalarial candidates, exploiting ACTs' advantages, molecular hybridization concept has been applied.[7] Hybrids combining artemisinin with other antimalarial drugs or bioactive compounds, via a linker, have been developed as promising antimalarial and anticancer agents.[8]



I

Based on recent studies which had generated artemisinin hybrids incorporating bile acid, cholesterol and estrogen moieties with significant antimalarial and cytotoxic properties,[9,10,11] we designed and synthesized a new series of artemisinin-steroid hybrid molecules **I**. Particularly, a C-10 non acetal artemisinin-derived carboxylic acid was conjugated with different modified steroidal alcohols, through an ester linkage. The artemisinin derivative presents great stability and bioavailability[12], while the steroidal fragments have been used by our research group in the synthesis of steroidal alkylating agents, which have exhibited important *in vitro* and *in vivo* anticancer activity.[13] The new hybrids were evaluated for their antileukemic activity against both sensitive CCRF-CEM and multidrug-resistant CEM/ADR5000 cells and showed interesting IC_{50} values. The most potent hybrids may serve as promising antileukemic agents.

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COMPUTER-ASSISTED SELECTIVE OPTIMIZATION OF SIDE ACTIVITIES – FROM CINALUKAST TO A PPARα MODULATOR

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The optimization of bioactive small molecules via systematic structure-activity relationship evaluation cycles is a time-consuming and expensive task. To overcome this issue, various techniques have evolved. Computational approaches for structural optimization are on the rise to minimize synthetic and experimental efforts needed to achieve suitable improvements[1]. Selective optimization of side-activities (SOSA)[2] – aiming at expanding weak side-target activities of approved drugs – also has great potential in speeding up the development of new drug candidates[3].

We intended to fuse these two strategies in a computer-assisted SOSA approach. We observed weak partial agonistic activities for cinalukast[4], a cysteinyl leukotriene receptor 1 ($CysLT_1R$) antagonist, on peroxisome proliferator-activated receptors (PPAR). The challenging and low-yielding synthesis of this compound and close derivatives made it a suitable candidate to evaluate whether automated analogue design and computational ranking could minimize the synthetic efforts and retrieve an optimized PPARα modulator.

For the lipid binding nuclear receptor PPARα, the HYDE[5] scoring appeared suitable and after promising proof-of-concept results, we applied it on an automatically generated virtual combinatorial library of approximately 8000 cinalukast analogues to discover superior PPARα ligands. The computationally favored molecules for PPARα binding retrieved from this workflow were further analyzed *in silico* for their binding mode and synthetic feasibility. A promising and favored hit was synthesized and tested *in vitro* which indeed revealed improved PPARα activity.

Our results show that the combination of employing a preferable lead structure according to the SOSA concept with automated computational optimization can enable rapid and cost-saving development of bioactive NCEs with favorable properties.

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ENCAPSULATION OF TYROSOL IN BIOCOMPATIBLE NANOCARRIERS AND OPTIMIZATION OF THE PROCESS USING EXPERIMENTAL DESIGN

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Nanotechnology is constantly gaining ground due to its broad spectrum of applications, ranging from agriculture to electronics. In medicine, one possible use is for the encapsulation of a bioactive agent in an appropriate carrier, aiming to higher absorption of the drug and higher specificity of the formulation.[1]

However, the properties of the occurring system are strongly affected by the choice of the nanocarrier, the size and the surface charge of the nanoparticles.[2] Therefore, it is of utmost importance to thoroughly investigate how different carriers and different methodologies for the preparation of the nanoparticles affect the properties of the final nanoparticulate system and identify the optimal conditions for the intended application.

In the present study, tyrosol (tyr), a natural antioxidant, with antiarrhythmic and cardiovascular activity[3], was encapsulated in various biocompatible and biodegradable carriers, namely the cyclic oligosaccharide β-cyclodextrin (β-CD)[4] and the natural polysaccharide chitosan[5]. The inclusion complexes of β-CD with tyrosol were synthesized using the kneading method whereas the formation of chitosan nanoparticles encapsulating tyrosol were prepared via the ionotropic gelation method. The nanoparticles were evaluated for their antioxidant activity, and were fully characterized concerning their size, ζ-potential, and polydispersity index, their thermal charateristics, and their structure and morphology using a wide variety of techniques (DLS, NMR, FT-IR UV-Vis, SEM, DSC, TGA).

In an effort to prolong the release rate of tyrosol from the nanosystem, the possibility to combine the two nanocarriers was explored using two different approaches: (a) the β-CD-tyrosol complex was coated with chitosan and (b) chitosan was modified by grafting β-CD and the resulting material was used for the encapsulation of tyrosol.

Multifactorial experimental design was applied for the optimization of the encapsulation process using the initial concentration of the polymer, the loading capacity and the amount of the cross-linking agent as independent variables. The morphological characteristics of the nanoparticles' dispersion were used as responses. The results were analyzed using the appropriate statistical tools, in order to identify the optimal preparation conditions and export a prediction model.

Acknowledgments

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SYNTHESIS OF NEW BENGAMIDE ANALOGUES AND ENCAPSULATION INTO THERMO-RESPONSIVE MAGNETIC NANOPARTICLES

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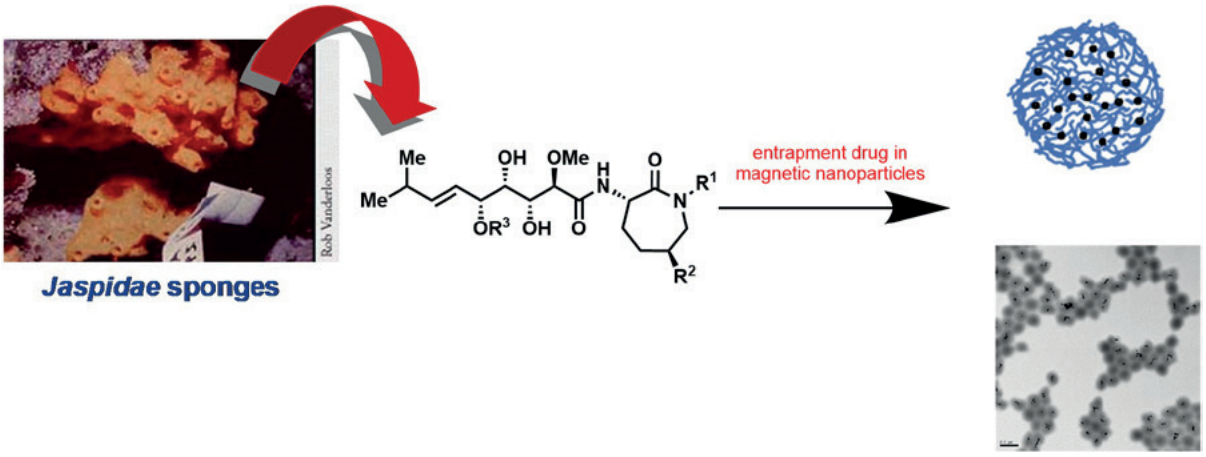
The development and identification of new antitumoral drugs has become a research area of great interest and maximum priority. Firstly, to overcome the secondary effects frequently shown by current antitumorals and, secondly, to prevent the appearance of tumours resistance to these agents. Marine sponges corresponding to the *Jaspidae* family have proved to be a prolific source of bioactive natural products[1]. Among these, the bengamides have showed an important biological profile, including antitumor, antibiotic and anthelmintic properties[2].

We describe here a study directed towards the total synthesis of bengamides including their encapsulation into temperature-sensitive microgels having magnetic Fe_3O_4 cores. Magnetic nanoparticles were prepared by the coprecipitation method and show an acrylic acid surface functionalization. We chose poly(*N*-isopropylacrylamide) (PNIPAM) as polymeric material, which was grown by a free radical polymerization process.

Key words: bengamides, *Jaspidae*, Antitumoral, analogues, total synthesis, magnetic nanoparticles.



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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL P2X7 INHIBITORS

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The P2X7 purinergic receptor is an ionotropic ligand-gated cation channel, activated by extracellular ATP, and an important upstream activator of NLRP3 inflammasome. To date, numerous classes of P2X7R antagonists have been generated featuring drug-like properties for the treatment of peripheral inflammatory diseases, displaying various chemical structures.[1] Moreover, the X-ray crystal structure of the homologous *z*P2X4 was revealed in 2009[2] and allowed the application of both ligand and structure based methodologies targeting the design and development of new drug candidates.

Inspired by the structure of adamantyl amide P2X7 antagonists, already reported in the literature, the current study focused on the development of novel P2X7 inhibitors, bearing nitric oxide or hydrogen sulfide donor groups that may enhance their anti-inflammatory activity.[3,4] Two generations were designed and synthesized. The first generation included adamantane-based amides and their bioisosteres 1,2,3-triazoles. In parallel, a ligand-based pharmacophore model indicated the structural features and substitutions required on the new analogues for effective inhibition of the receptor.

The second generation aimed to replace adamantane with scaffolds that could improve the blocking activity of the novel compounds. Additionally, the determination of the crystal structures of a mammalian P2X7 receptor (*Ailuropoda melanoleuca*, giant panda) in 2016,[5] which presents comparable characteristics to the human P2X7R, allowed the construction of a homology model, in order to study the crucial interactions for effective binding to the receptor.

The functional biological evaluation of the potential P2X7R synthesized antagonists was based on electrophysiological analysis, which included two-electrode voltage-clamp experiments, using *Xenopus laevis* oocyte-expressed human P2X7 receptors, activated with ATP.[6]

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CELLULAR ACTIVITY OF NEW HALF-SANDWICH Os(II) AND Ru(II) BATHOPHENANTHROLINE COMPLEXES IN HIGHLY INVASIVE TRIPLE-NEGATIVE BREAST CANCER CELLS

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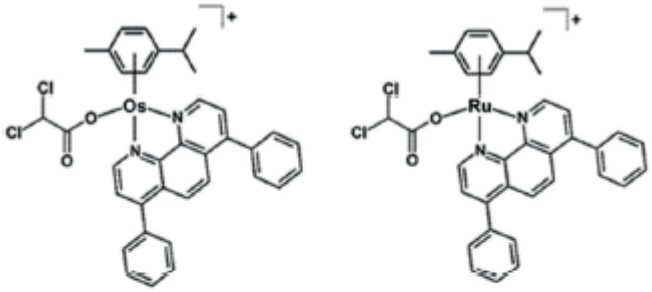

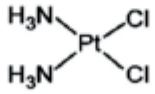

Despite the clinical success of platinum-based chemotherapeutics, significant research efforts have focused on developing compounds based on other metals[1]. In recent years, there has been particular interest in the development of ruthenium and osmium based drugs, and several have been shown to exhibit anticancer activity [2]. However, the mechanism of action of these organometallic complexes is not yet fully understood.In this work the effect of two, recently developed metal-based half sandwich complexes [Os(η6-pcym)(bphen)(dca)]PF6 (Os-dca) and [Ru(η6-pcym)(bphen)(dca)]PF6 (Ru-dca) [bphen = 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline); dca = dichloroacetate][3] was tested on triple-negative breast cancer cells (TNBCs). TNBCs belong to a highly invasive breast cancer subtype characterised by lack of estrogen (ER-), progesterone (PR-), and HER2 (HER2-) receptors, so the new therapies for this malignancy are needed[4]. The investigated compounds showed very potent cytotoxic activity in TNBCs and were much less toxic in noncancerous cell lines. Plausibly, both Os-dca and Ru-dca were able to reduce the metastases related properties of the TNBCs, such as migration, invasion, and re-adhesion. It was found that these effects are likely associated with the ability of these compounds to suppress MMP-9 activity and/or production. Moreover, the reduced expression of AQP5 could also contribute to these anti-metastatic effects in the case of Os-dca. Especially, Os-dca is a potential candidate for further testing as chemotherapeutic agents for hardly treatable human TNBCs.

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ROS101, A NOVEL HYDROGEN PEROXIDE ACTIVATED METHOTREXATE PRODRUG: SYNTHESIS, IN VITRO, AND IN VIVO EVALUATION

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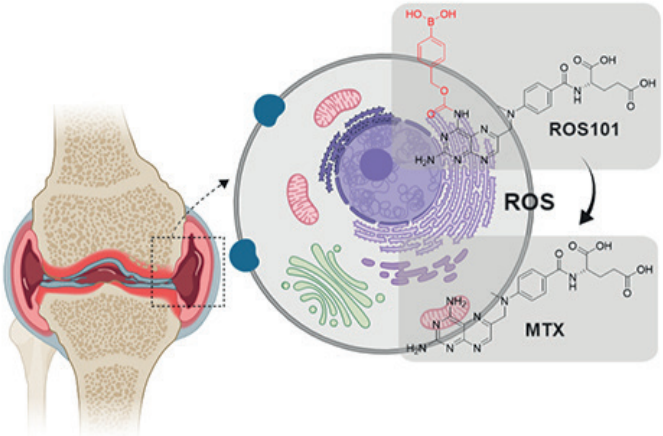
Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joints damage and other extra-articular manifestations.[1] Despite the efficacy of low-dose methotrexate (LD-**MTX**) in RA treatment, its adverse effects are the predominant reasons for discontinuation of therapy.[2] As a therapeutic strategy, the presence of increased concentrations of reactive oxygen species (ROS) in the inflammatory environment can serve as the stimulus for prodrug activation in site-selective drug delivery systems. Herein, we present **ROS101**, a new arylboronic acid-ROS-sensitive prodrug of **MTX** for site-selective delivery to inflammatory tissue associated with RA, *e.g.* the synovial membrane, with the aim of reducing side effects in RA therapy.[3,4]

We describe the synthesis of **ROS101** with an high overall yield. Moreover, we investigated the effect and toxicity of **ROS101** in a rat collagen induced arthritis (CIA) model of RA, finding that **ROS101** can induce efficacy in the treatment of RA at an equimolar dose compared to **MTX**, while avoiding adverse effects known to restrict treatment with **MTX**. To further characterize **ROS101** activity and its ROS mediated activation to **MTX**, we investigated cell viability and cytotoxicity in the presence of the ROS scavenger pyruvate, as well as **ROS101** stability in buffer and cell media, finding a correlation between ROS concentration and **ROS101** activity. Moreover, the *in vitro* ADME properties of **ROS101** were investigated, including oral absorption, rat plasma, and microsome stability.



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DESIGN AND SYNTHESIS OF MULTISUBSTITUTED 1,2,3,4-TETRAHYDROPYRIMIDINES AS NOVEL ALLOSTERIC MODULATORS TARGETED TO THE C1 DOMAIN OF PKC

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Protein kinase C (PKC) isoforms represent highly attractive drug targets as they modulate numerous cellular functions including metabolism, growth, apoptosis and differentiation.[1] Utilizing the crystal structure of the PKCδ C1B domain (PDB ID: 1PTR),[2] we have developed and previously reported hydrophobic isophthalic acid derivatives which allosterically modulate PKC activity by targeting its C1 domain.[3, 4] Recently, we synthesized and characterized the binding affinities of a series of multisubstituted pyrimidines as isophthalate analogs.[5] In contrast to our docking experiments, scaffold hopping from a phenyl to a pyrimidine core diminished the binding affinity of the compounds. However, since phospholipid bilayers play a key role during PKC activation, a deeper investigation with molecular dynamics simulations suggested that non-favorable ligand-bilayer interactions may contribute to the diminished affinity of those pyrimidine derivatives.[6] Based on the new insight, in the present study, we designed and synthesized a set of 1,2,3,4-tetrahydropyrimidines as novel derivatives targeting the C1 domain.

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COVALENT ISOTHIOCYANATE INHIBITORS OF MACROPHAGE MIGRATION INHIBITORY FACTOR AS POTENTIAL DRUG LEADS

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Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine with well-characterized roles in the innate immune response. MIF is overexpressed in various cancers, such as colorectal cancer, pancreatic cancer, leukemia, prostate cancer, and breast cancer as well as inflammatory diseases including acute pancreatitis and rheumatoid arthritis. MIF binds to the transmembrane domain of CD74 to induce a signaling cascade of cell proliferation and survival. MIF possesses keto-enol tautomerase activity against dopachrome and phenylpyruvate with the N-terminal proline as the catalytic active site, however, no physiological substrates of MIF have yet been identified. Small molecule inhibitors of MIF have been identified with the potential for treating inflammatory diseases and other disease pathologies. Isothiocyanates (ITCs) are compounds found in cruciferous vegetables and are irreversible inhibitors of MIF's tautomerase activity via covalent attachment to the N-terminal catalytic proline of MIF.

We expressed recombinant human MIF (rhMIF) in *Escherichia coli* to test the tautomerase activity of novel synthetic ITCs. We investigated benzyl ITC derivatives with sulfonamide and benzodioxole moieties, expanding the structure-activity relationships by extending the linker length between the benzene ring and ITC moiety and its effect on MIF tautomerase activity. Initially, five new ITCs were synthesized and rhMIF biological assays and the best two compounds (**2** & **3**) gave IC_{50} values of 0.72 ± 0.06 and 0.44 ± 0.06 μM respectively. We found that the activity of ITCs with sulfonamide substituent increased with a longer linker length. However, no increase in activity was observed in the benzodioxole series. Further investigation on sulfonamide derivatives has identified compound **10** with low nanomolar activity in MIF tautomerase assay. Inhibitors with good *in vitro* enzyme activity were tested against colorectal cancer cell lines using resazurin reduction assay. Cell viability assays of compounds **2** & **10** against CT26 colorectal cancer cell lines have shown promising activity with IC_{50} values of 1.45 ± 0.06 and 1.92 ± 0.03 μM respectively for 24 h of incubation. Preliminary studies have also indicated that ITCs may reduce the severity of experimental acute pancreatitis. In summary, ITCs show promise as drug leads for colorectal cancer and pancreatitis.

SYNTHESIS OF NOVEL CARBOHYDRATE DELIVERY AGENTS FOR BORON NEUTRON CAPTURE THERAPY

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First proposed in 1936,[1] boron neutron capture therapy (BNCT) is a promising radiation technique that has previously been used for the treatment of high-grade gliomas, primary/metastatic melanomas and recurrent cancers in the head and neck region.[2] BNCT involves the selective uptake of boron containing delivery agents in cancer cells, followed by the irradiation of the cells with a neutron beam. This results in a nuclear reaction whereby ^{10}B atoms absorb low energy thermal neutrons and break up to form ^{4}He (α-particle), ^{7}Li and gamma radiation.[3] The radiation leads to the lysis of the tumour cell and as the α-particles can only travel a maximum of 5-9 μm in tissue[3], no adjacent healthy cells are destroyed in the process. This makes BNCT a highly selective technique when compared to current chemotherapy treatments.

While promising, the limitations of the current boron delivery agents in clinical use are hampering the potential breakthroughs and widespread use of this treatment. We have been working on the synthesis and biological testing of improved delivery agents based on glycoconjugates. At the conference, our most recent results on this topic will be presented.

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DESIGN AND ASSESSMENT OF SMALL MOLECULE EZH2 INHIBITORS

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Epigenetic pathways are recognized as determinants to cancer development and progression. Polycomb repressive complex 2 (PRC2) is an epigenetic regulator that catalyzes the trimethylation of lysine 27 in Histone 3 (H3K27me3), a process that facilitates chromatin compaction and gene silencing.[1] The overexpression of Enhancer of zeste homolog 2 (EZH2), the catalytic subunit of PRC2, is implicated in the development and progression of a variety of cancers with poor prognosis. Thus, the therapeutic targeting of EZH2 has attracted significant attention for the development of selective small molecule inhibitors.[2]

To contribute to the discovery of EZH2 small molecule inhibitors, we carried out a computer-aided drug design (CADD) campaign. First, a panel of unique 3D-pharmacophore models were generated, validated, and optimized using LigandScout Advanced 4.2.1 software to support hit finding.[3] The results show valuable information about the key interactions and the 3D-geometries associated with inhibition of EZH2 activity. The prioritized models were used in two hit finding campaigns: virtual screening and *de novo* design. Using the unique 3D-pharmacophore-based virtual screening method (iscreen) from LigandScout, several databases (*e.g.*, DrugBank, NCI, MuTaLig Chemotheca, and our in-house libraries) were computed and screened. The interesting virtual hit molecules with high inhibition potential totalled more than 60 compounds which have been evaluated *in-vitro* in a variety of assays. These studies are being benchmarked against two EZH2 inhibitors, one of them currently in clinical trials. Many of the putative EZH2 hits from the *in-silico* studies have been shown to have acceptable off-target and ADME-Tox profiles. The profiling of these compounds in biochemical and cell-based EZHZ assays is currently underway.

In parallel to the above, we started a *de novo design* campaign based on selected pharmacophore models and new scaffold cores for EZH2 inhibition have been identified. The structures obtained from *de novo design* are now being synthesized for validation *in-vitro* using the EZH2 and ADME-Tox assays.

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SYNTHESIS OF FUNCTIONALIZED PROBES TO IDENTIFY AND VALIDATE NOVEL THERAPEUTIC AND DIAGNOSTIC TARGETS FOR DRY EYE DISEASE AND IRRITABLE BOWEL SYNDROME

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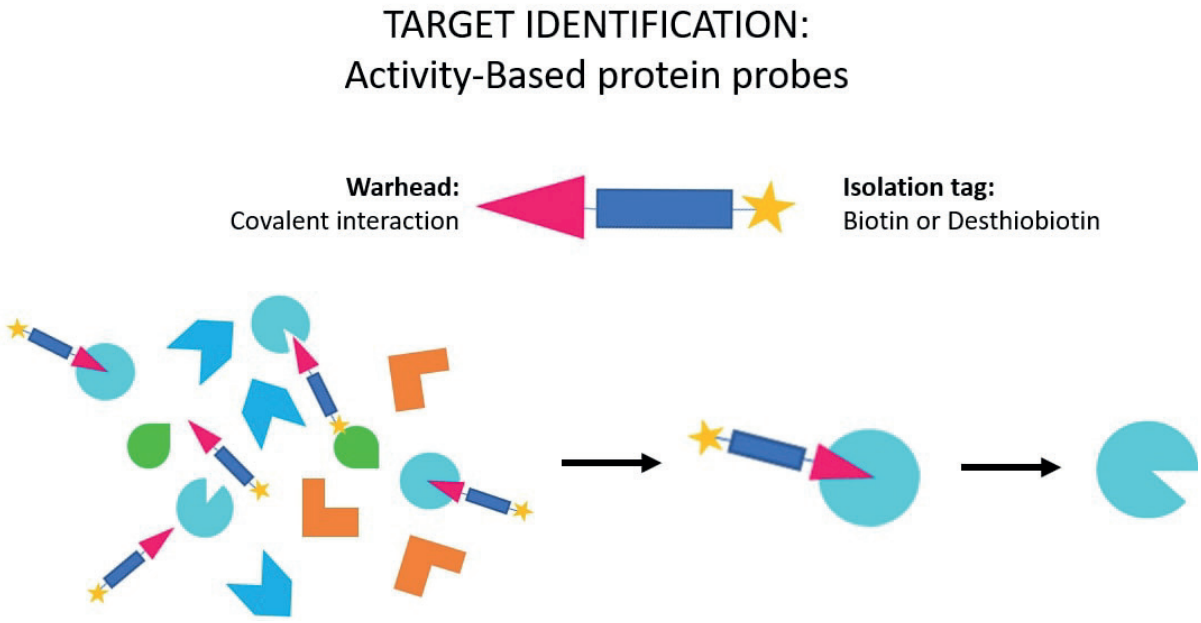
Serine proteases are a subgroup of the protease family involved in several physiological processes, including immune response, cell death and tissue healing. [1] The upregulation of these proteases can increase inflammatory cytokines, degradation of extracellular matrix components, activation of PAR2 or MMP-9, among others. [2,3]

We recently obtained an *in vivo* proof of concept with a multi-target serine protease inhibitor in Dry Eye Disease (DED). Topical application of this compound in the eye of a tear-deficient dry eye rat animal model gave a significant reduction of both tissue damage and of inflammatory parameters. [4] Moreover, serine protease inhibitors also cause a decrease in visceral hypersensitivity in a rat model of post-inflammatory visceral hypersensitivity. [5] Therefore, we hypothesized that serine proteases play an important role in both DED and Irritable Bowel Disease (IBS).

In order to characterize the proteases involved in DED and IBS, a series of serine protease-targeted activity-based probes (ABPs), analogues from our inhibitors, have been synthesized. The probes were designed to target chymotrypsin, trypsin, and elastase-like serine peptidases, with biotin or desthiobiotin as reporting tag and a diaryl phosphonate as a warhead. The synthesis of ABPs with a basic side-chain amino acid analogue was quite challenging and required extensive optimization of the synthetic route. We will also report on the potency of these probes on a few isolated serine proteases.



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COMPUTATIONAL METABOLITES PREDICTION AND TOXICOLOGICAL EVALUATION OF RECENT LAUNCHED ANTINEOPLASTIC DRUGS

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Nonclinical evaluation of drug safety usually include assessment of drug exposure, primarily parent drug plasma concentration and animal toxicology studies. These safety analysis usually is sufficient when the metabolic profile in humans is similar to that in at least one of the animal species used in nonclinical studies. However, metabolic profiles can vary across species both quantitatively and qualitatively. In addition, there are cases when clinically relevant metabolites have not been identified in analytical methods due to the metabolite is formed only in humans or if the metabolite is present at disproportionately higher levels in humans than in the animal species. Since it is not mandatory for drug metabolites to be evaluated separately in a cross-species, their specific contribution to the overall drug toxicity has often remained unknown and nonsufficient [1]. Toxicological studies of drugs metabolites become urgent for drugs with high exposure and elevated toxicity, as antineoplastics [2]. Bearing this in mind, computational studies were conducted to predict and evaluate metabolites of antineoplastics drugs recently launched by FDA [3]. Computational analysis were based on artificial intelligence in order to predict toxicological risks of antineoplastics metabolites [4]. A total of seventy metabolites (60 predicted and 10 described in literature) were analysed. In silico risk assessment indicated that around 86% of the metabolites were assigned with reproductive toxicity, 69% were assigned as carcinogenicity in rats and mice, 10% were predicted with mutagenicity and 6% of metabolites presented hepatotoxicity risks. In view of these results, it was possible to attest that there are potential toxic metabolites, which are not considered for safety assessments since they are not pharmacologically active. Herein, the computational approaches were successfully applied in prediction and toxicological evaluation of antineoplastics metabolites highlighting the relevance of the recommendation of chemical elucidation and safety evaluation of drug metabolites by regulatory agencies.

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RISK ASSESSMENT OF CANNABINOIDS DEGRADATION PRODUCTS USING IN SILICO APPROACH

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The most abundant cannabinoids present in the *Cannabis* plant are Δ9-tetrahydrocannabinol (THC), the main psychoactive compound, and cannabidiol (CBD) [1]. CBD was the first FDA approved drug from *Cannabis* plants for the treatment of seizures associated with rare syndromes, without psychotropic effects and abuse liability [2,3]. The degradation product of THC, cannabidinol (CBN) does not occur naturally in the plant and acts as sedative and anticonvulsant that is anti-inflammatory [4]. According to the International Conference on Harmonization (ICH), it is of fundamental importance that the mechanisms governing degradation of newly developed long-term use drugs are well understood. It is also essential that the identity of the degradation products (DPs) and their potential toxicities are characterized [5]. In this context, the goal of this study was to evaluate the potential toxicities of degradation products of the most common cannabinoid presented in cannabis strains: cannabidiol (CBD) and cannabinol (CBD) employing *in silico* techniques. Considering stress testing, the predictions of DPs resulted in a total of 26 and 7 DPs for CBD and CBD, respectively. *In silico* risk assessment were obtained using ADMET predictor® and indicated that: (1) all CBD_DPs (1-26) and CBN_DP3, CBN_DP4, CBN_DP5, CBN_DP6 and CBN_DP7 were predicted with hepatotoxicity risk, since these DPs presented a potential in elevating serum levels of liver enzymes used in the diagnosis of liver injury; (2) mutagenicity was predicted for CBN_DP3 e CBN_DP4, based on Ames test; (3) hERG inhibition, an indicative of cardiotoxicity, was predicted for CBN_DP5, CBN_DP6 and CBN_DP7; (4) acute toxicity in rats was predicted for all CBD_DPs (1-26) and CBN_DP5, CBN_DP6 e CBN_DP7, since these DPs presented LD50 < 300mg/kg; (5) all CBD_DPs (1-26) and CBN_DPs (1-7) were predicted with reproductive toxicity, since they may be related to anything that disturbs the reproductive process of organisms, including adverse effects to sexual organs, behaviour, ease of conception, and developmental toxicity of offspring both before and after birth. Finally, (6) carcinogenicity, an important analysis for prediction of cancer induction, was assigned to CBD_DPs (1-26) and CBN_DPs (5-7). With these toxicity results, there is a necessity to avoid the degradation and, for this purpose, encapsulation with nanosystems will be developed. Then, to identify the best polymer for nanoencapsulation, simulations with different polymers are in progress.

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DEVELOPMENT OF NOVEL NS2B/NS3 PROTEASE INHIBITORS AGAINST THE DENGUE AND ZIKA VIRUSES

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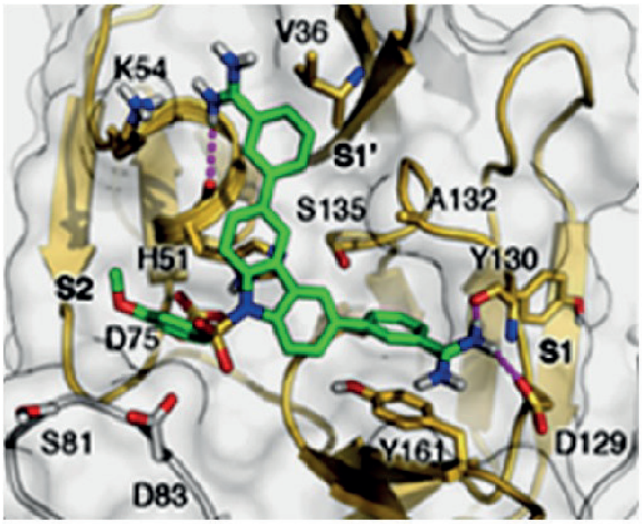
The Flaviviridae family includes viruses such as dengue, zika, yellow fever and West Nile for which there are currently no treatments available and constitute an unmet medical need for more than 2 billion people living in tropical and subtropical areas. In this case, small-molecule antivirals appear as the most promising approach especially since vaccine development is confounded by cross-reacting antibodies. Prompted by the conserved nature of the viral NS2B/NS3 protease across all flaviviruses we pursued development of small molecule pan-flaviral inhibitors. Starting with an earlier urea-bis-amidine hit we performed a scaffold hopping exercise which led to a carbazole bis-amidine with DENV2pro IC_{50} 1.16 uM and ZIKVpro IC_{50} 0.52 uM. Targeted SAR yielded several low toxicity carbazole bis-amidines with significant cellular activity against both DENV and ZIKV. In order to improve the solubility and permeability in our series we identified appropriate pro-drugs through bioisosteric replacement of the amidine groups with amidoximes. Our best current lead exhibits potent dual inhibition, increased safety (SI>140 μM) and significant cell-efficacy against both DENV2 and ZIKV (EC_{50} 0.35 and 7.78uM respectively). This is one of the best profiles among all published NS2B/NS3 protease inhibitors in the literature and constitutes a significant advancement towards a pan-flaviviral protease inhibitor.



CREATING DIVERSITY FROM BIOMASS: CHEMOSELECTIVE TANDEM BIO- AND METAL CATALYSIS FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED FURANS

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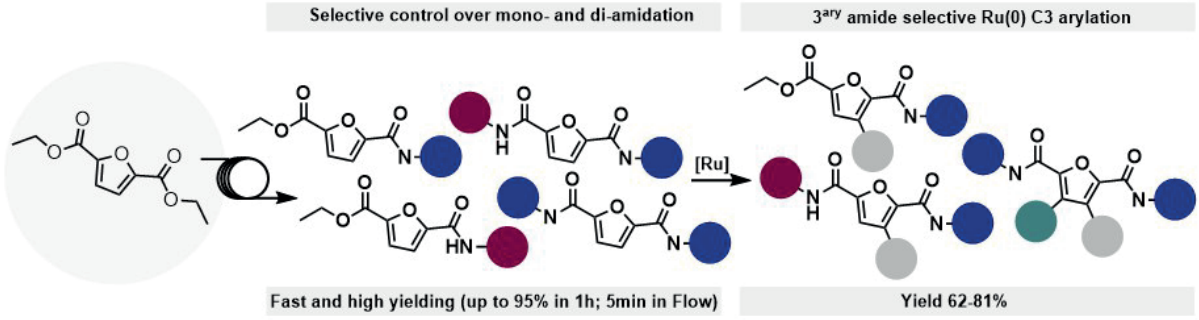
The synthesis and valorization of biomass-derived intermediates such as 5-hydroxymethylfurfural (HMF), 2,5-dimethylfuran, and 2,5-furandicarboxylic acid (FDCA) have been employed to access an extensive variety of chemical scaffolds. Given its rich chemistry and availability, HMF-derivates are undoubtedly a promising platform for the synthesis of small molecules for drug discovery in a diversity-oriented manner[1], following the lead of furan-containing FDA-approved molecules in the market such as ranitidine (anti-hipertensive), furosemide (diuretic), nitrofurantoin or cefuroxime (anti-bacterial). Yet, the synthetic access to promising more complex hetero-substituted furans, namely tri- and tetra- substituted still presents several limitations, namely the need for a complex substrate and low tolerability and diversification capability. Such endeavor automatically calls for need towards the development of novel and environmentally benign processes which allow direct chemoselective functionalization of easily accessible furans, namely from biorefinary.

Driven by the obvious advantages of bio- and modern transition metal catalsysis (TMC), the combination of both represents a privileged tool for substructure diversity-oriented synthetic strategies towards the construction of both nature-inspired and phamacologically active compounds. [2] The usage Ru^0 directing groups in furfural and HMF derivates have been reported by our group, amongst others, to, for instance, direct C3 arylation and addition of vinylsilanes to furfural imines, as well as C3 vinylation of N-methylfuran-2-carboxamide using vinylsilanes.[3]

Herein we report a tandem and two-step diversity oriented synthesis of furan-based scaffolds, based on a fast and high yielding biocatalysed amidation (5 minutes 95% yield) of biomass derived FDCA and chemo and regioselective C3-arylation via a tertiary amide hotspot. [4]



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HETEROARYL RADICAL REACTIONS ON PYRIDINSULFONAMIDE DERIVATIVES: ACCESS TO BIPYRIDINES AND/OR BIPYRIDIN SULTAMS

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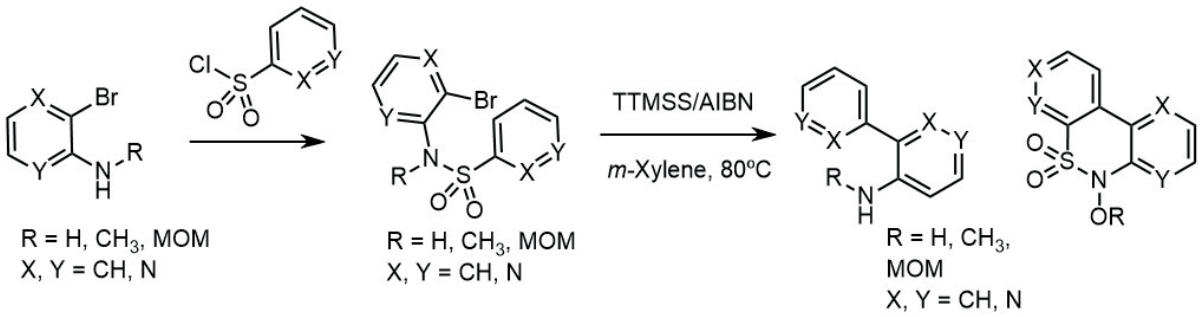
In light of pioneering reports of Motherwell, Curran and Chatigilialoglu, among de other,[1] the reactions of synthesis of biaryls, via intramolecular a free radical process have been well documented. Scarcely attention has been devoted to the preparation of bisheterocycles and however are nuclei widely represented in interesting molecules.

Here report our studies in the intramolecular addition of pyridyl radicals onto another pyridine, interconnected by a linker containing a sulfonamide, using transition-metal free methodology, in the presence of tris(trimethylsilyl)silane (TTMSS) and azobisisobutironitrile (AIBN) in the preparation of aminobipyridines y/or bipyridin sultams (Scheme 1).



Both of these cores are important motifs in natural product and therapeutic active derivatives. In addition, we communicated how the protecting group MOM, (methoxymethyl acetal) would provide unsubstituted or easily accessible unsustituted derivatives.

We gratefully acknowledge FEDER funds and Comunidad de Madrid (CAM, project B2017/BMD-3688 MULTI-TARGET&VIEW-CM FEDER FUNDS), Ministerio de Economia, Industria y Competitividad (project CTQ2017-85203-P), Instituto de Salud Carlos III (FEDER funds, ISCIII RETIC REDINREN RD16/0009/0015 FEDER FUNDS) and Universidad de Alcalá (CCG2017/EXP-021 and CCG2018/EXP-051) for financial support. J. R. thanks also the Universidad de Alcalá for a predoctoral grant.

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DESIGN AND SYNTHESIS OF SELECTIVE MUSCARINIC M2 RECEPTOR AGONISTS

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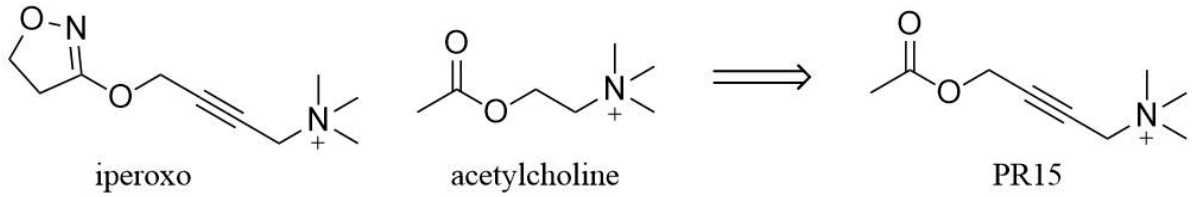
Muscarinic receptors play a vital role in the regulation of many peripheral and central functions in the human physiology. As the orthosteric binding site is highly conserved among all five muscarinic receptor subtypes, it is difficult to synthesize selective agonists. [1]

The crystal structure of the active M2 receptor bound to the superagonist iperoxo provides valuable insights into receptor-ligand interactions and conformational changes upon receptor activation. In the small orthosteric binding pocket iperoxo shows a bent shape. Two major interactions with the receptor are associated with the high affinity of iperoxo: a salt bridge between the quaternary ammonium group and the carboxylate function of Asp $103^{3.32}$ and hydrogen bonding between the isoxazoline oxygen and the side chain of $Asn404^{6.52}$. [2]

Based on these findings, we performed computational docking and synthesized a series of structural hybrids including PR15. The compounds are related to iperoxo and typical muscarinic agonists such as acetylcholine. We aimed to find how, variations of the alkyne linker and the isoxazoline head group of iperoxo will modify M2 receptor binding. Here we describe the synthesis, binding affinities and SARs of such compounds.



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DDX3X HELICASE INHIBITORS AS A NEW STRATEGY TO FIGHT THE WEST NILE VIRUS INFECTION

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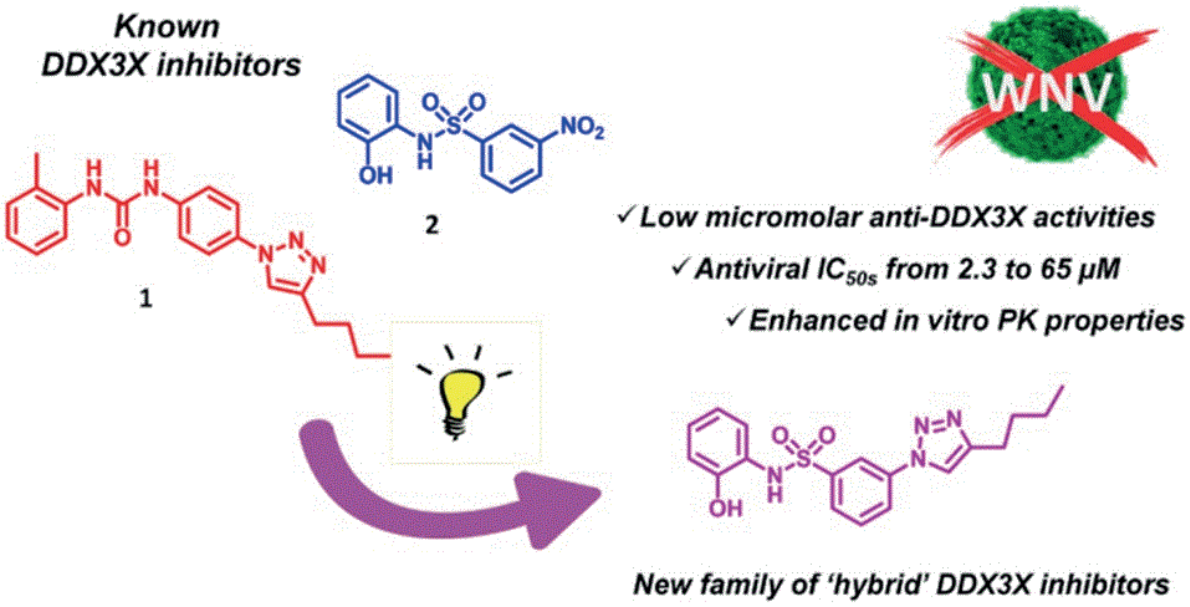
Increased frequency of arbovirus outbreaks in the last 10 years represents an important emergence for global health. Climate warming, extensive urbanization of tropical regions, and human migration flows facilitate the expansion of anthropophilic mosquitos and the emerging or re-emerging of new viral infections. Only recently the human adenosinetriphosphatase/RNA helicase X-linked DEAD-box polypeptide 3 (DDX3X) emerged as a novel therapeutic target in the fight against infectious diseases. Herein, starting from our previous studies, a new family of DDX3X inhibitors was designed, synthesized, validated on the target enzyme, and evaluated against the West Nile virus (WNV) infection. Time of addition experiments after virus infection indicated that the compounds exerted their antiviral activities after the entry process, likely at the protein translation step of WNV replication. Finally, the most interesting compounds were then analyzed for their in vitro pharmacokinetic parameters, revealing favorable absorption, distribution, metabolism, and excretion values. The good safety profile together with a good activity against WNV for which no treatments are currently available, make this new class of molecules a good starting point for further in vivo studies.



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MICROWAVE-ASSISTED MULTICOMPONENT CASCADE: GEWALD REACTION FOLLOWED BY A GBBR CYCLIZATION FOR THE SYNTHESIS OF NOVEL THIOPHENE[3,2-D]PYRIMIDINE DERIVATIVES AS POTENTIAL ANTIMICORBIAL AGENTS

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The worldwide increase of multidrug resistant (MDR) and extensively drug resistant (XDR) strains of microorganisms, such as *Staphylococcus aureus* and *Mycobacterium Tuberculosis*, among the most lethal infectious agents affecting mankind, together with the lack of new effective drugs in the last decades, suggested the urgent need for the identification of innovative antimicrobial targets and inhibitors. [1]

Referring to SAR previously reported in recent works [2,3], the *Gewald* and the *Groebke-Blackburn-Bienaymé* multicomponent reactions [4] were here applied in a microwave-assisted cascade to synthesize a library of new thiophenes derivatives as potential antimicrobial agents. Starting from commercially available materials, in just three steps we were able to introduce three different sites of diversification and afford the respective products with yields ranging from moderate to very good. Desired aromatic and aliphatic substituents were thus inserted into the scaffolds, in order to modulate their hydrophobicity, water solubility, and exploring the steric hindrance around the main core.

A library of hit compounds was therefore developed, and subsequently submitted to the San Paolo Hospital in Milan for *in vitro* screening tests against the most common MDR strains.

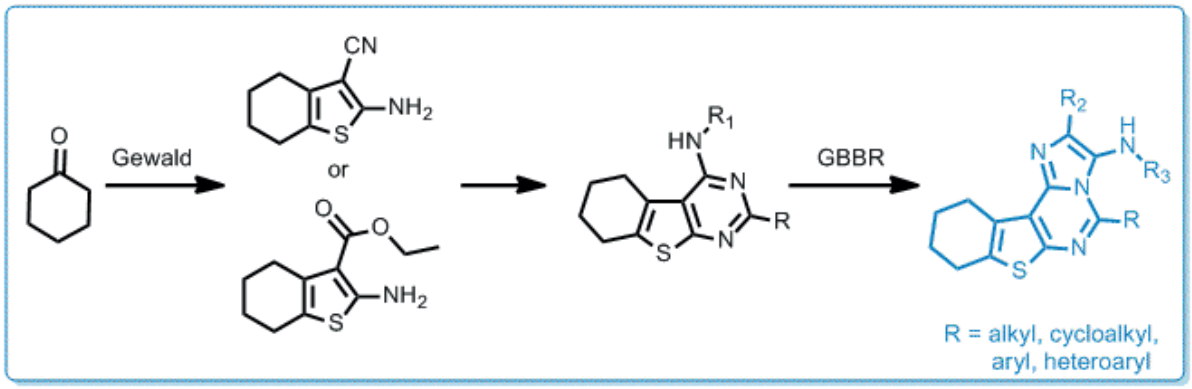

Figure 1. General scheme for the designed thiophene[3,2-d]pyrimidine derivatives.

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RUTHENIUM-CATALYZED HYDROGEN BORROWING SYNTHESIS OF PEG FUNCTIONALIZED AMINES

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Organic amines play a central role in pharmaceutical synthesis, due to their frequent occurrence in commercially available monomers and their effect on the physicochemical properties of drugs.[1] Hydrogen borrowing is a powerful and atom economical approach for carbon-nitrogen bond synthesis, however, polyethylene glycols (PEG), low toxicity and eco-friendly poly-ether alcohols, are previously unknown to participate in the reaction. In this presentation we report the first direct *N*-PEGylation of aliphatic and aromatic amines via hydrogen borrowing reductive amination using the Williams Catalyst, [Ru(*p*-cymene)Cl_2]$_2$, operating under relatively mild conditions and without exogenous base. A broad scope of amine nucleophiles was tolerated and strong inverse correlation between reaction rate and PEG chain length was observed. The reaction provides an exciting new method for the convenient and mild PEG functionalization of amines of biological and pharmaceutical interest.

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GREEN APPROACHES FOR THE SYNTHESIS OF NUCLEOTIDES, THEIR CONJUGATES AND ANALOGUES

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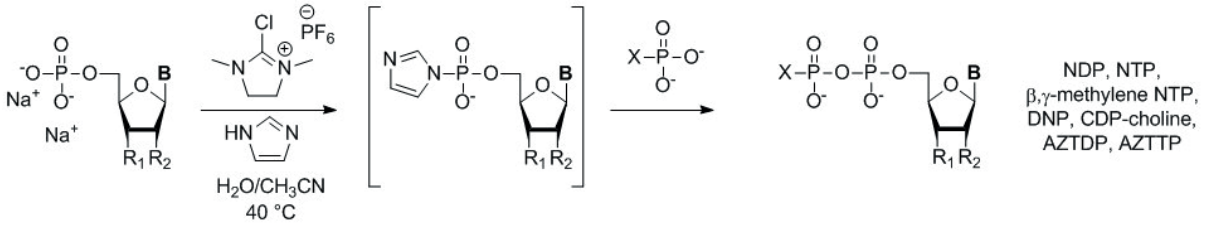
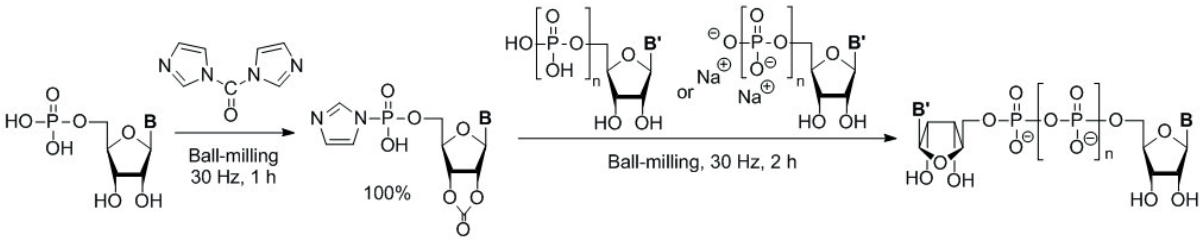
Given the importance of nucleotides and their derivatives in biological processes, numerous methods have been developed to access to these compounds and their structural analogues.[1] Their scope ranges from mechanistic probes to versatile chemical tools for assay development and biomedical applications. Most of these syntheses present important drawbacks, such as the use of non-volatile and harmful solvents (DMF, pyridine), preparation of substrates or phosphorus reagents in their alkylammonium form due to solubility issues, anhydrous conditions, and fastidious purifications.

We have developed original one-pot, protecting-group free approaches, which are user-friendly and reliable, for nucleotides starting from nucleoside 5'-monophosphates and through phosphorimidazolide intermediates. Both methods present convenient set-up, i.e. non-dry solvent and reagents, substrates in their sodium or acid form, and commercially available and cheap phosphorus reagents as sodium or potassium salts. The first strategy uses 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate and imidazole as activating agents in a water medium, and allows to access a variety of nucleosides 5'-polyphosphates as well as conjugates and analogues.[2]



The second strategy is a solvent-assisted mechanochemical approach, which allows to prepare symmetrical and mixed dinucleoside 5,5'-polyphosphates.[3] Under ball-milling conditions, nucleoside 5'-monophosphates are quantitatively activated using the eco-friendly *N,N'*-carbonyldiimidazole into their phosphorimidazolide derivatives. The addition of a nucleoside 5'-mono, di or triphosphate directly leads to the formation of the corresponding dinucleotides. Other benefits of this one-pot method include short reaction time, high conversion rates and easy set-up and purification. This work offers new perspectives for the synthesis of nucleotide conjugates and analogues, combining the phosphorimidazolide approach and milling conditions.



Since phosphorimidazolides are essential intermediates for pyrophosphate bond formation, our studies offer new perspectives for the development of greener approaches to access a wide range of nucleotide derivatives and analogues.

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NEW HIGH POTENT ACYCLIC NUCLEOTIDE ANALOGS AGAINST DNA VIRUSES

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Among antiviral drugs, acyclic nucleoside phosphonates (ANPs) represent prominent class and their functionalization targeting better bioavailability has attracted considerable attention. Tenofovir (bis(POC)-PMPA), cidofovir (HPMPC) and adefovir (bis(POM)-PMEA) are three approved antiviral drugs of the class of ANP, which are still intensively investigated under their prodrug forms to reach better or new biological activity. Although these ANPs improve their pharmacokinetic and antiviral performance, they suffer of some toxicity and they were found inactive against nucleoside resistant viral mutants then is still relevant to develop new ANP scaffold. Herein we report the biological properties of a new family of ANP which possess antiviral activity in nanomolar range against DNA viruses. Among them, LAVR-289 was evaluated with the technology ANCHOR by Dr. F Gallardo (NeoVirTech, Toulouse) and the table hereafter reports the potent in vitro activity of LAVR-289 in comparison with relevant compounds for cell activity studies. LAVR-289 is active against Herpesvirus (hCMV, HSV, VZV), Adenovirus, Poxvirus and (FHV, MYXV, EHV). LAVR-289 was also evaluated against VZV in human skin organ culture and in vivo using SCID-Hu skin mouse model of VZV (efficacy, virus spread, toxicity, dose & schedule, delay treatment and durability, …), and results from the experiments gave substantial credence to the developing program (collaboration Pr. J. Moffat - Department of Microbiology and Immunology, NIH, NIAID, USA).[1]

Viral Family	Virus	LAVR-289	Cidofovir	Ganciclovir	Foscarnet	Acyclovir	Maribavir	Letermovir
Herpes	hCMV	0.04	0.4	3.8	50-800	>200	0.31	0.005
	HSV-1	0.2	3.0	0.7	92-95	3.8	inactive	>10
	HSV-2	0.2	6.5	2.5	91-96	4.4	inactive	>10
	VZV	0.007	0.5	1.3	39.8	3.6	inactive	>10
Adenovirus	hAdV-B7	0.08	1.3	4.5-33	inactive	>100	-	-
Pox	VV	0.05	46	>392	inactive	>144	-	-
	VV TK-	0.01						

hCMV: human cytomegalovirus; HSV-1 & HSV-2 : herpes simplex virus type 1 and 2; VZV: varicella zoster virus; hADV-B7: human adenovirus type B7; VV: vaccinia virus. **Potency expressed as EC_{50} = concentration in µM** required to reduce viral replication by 50% in vitro. "-" indicates no data. Valganciclovir and Brincidofovir are rapidly converted in vivo to ganciclovir and cidofovir, respectively, which are the relevant compounds for cell activity studies.

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HET-ARYNE COUPLING: TOWARDS TRANSITION-METAL-FREE «GREENER» HETEROBIARYL SYNTHESIS

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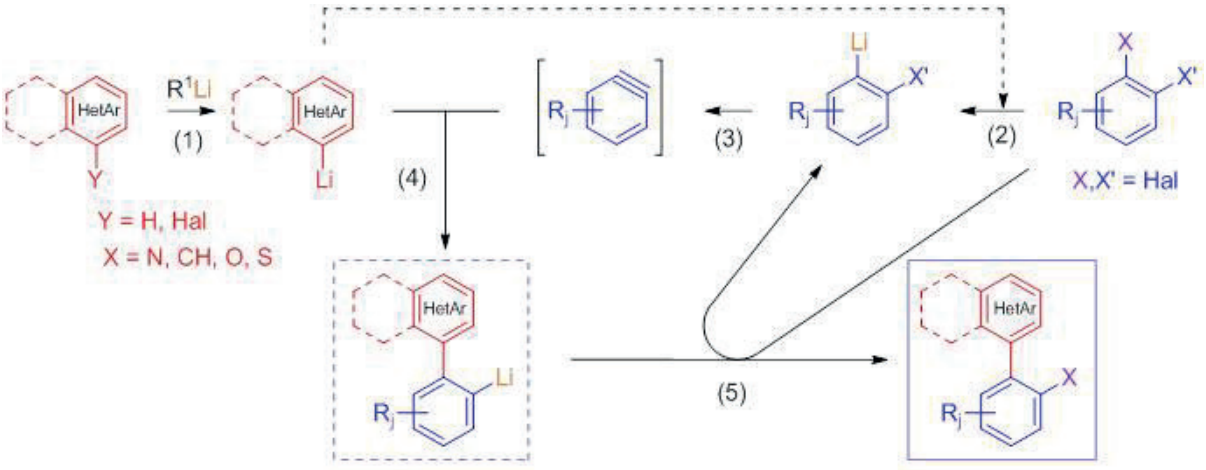
More than a century ago, Pasteur developed the first method to separate a single enantiomer from its racemic one and since then, interest in chiral compounds has continued to increase. Actually, about one out of 20 pharmaceutical products contains biarylic moities exhibiting axial chirality. Most of the synthesis methods of aryl-aryl link are based on cross-coupling reactions which require the use of transition metals and result in significant contamination problems for the pharmaceutical industry. Thus, we aim to develop in this study a new method to form heteroaryl-aryl bonds using organolithium as key reagent, which is easier to remove and less toxic for the organism.

Our results report the arylation of heterocycles using a transition metal-free "HetAryne coupling" reaction, as well as the effect of ligands and salt on the coupling reaction. Our findings underline the remarkable effect of additives (salts, ligands) on the coupling reaction and the efficiency of this route to construct hetaryl-aryl backbones and to lead to a wide range of heterobiaryl structures using the novel “Het-Aryne” route.

Finally, we extend this new pathway to form axially chiral heterobiaryls by developing an atropo-enantioselective version of the Het-Aryne coupling using hindered heterocyclic coupling partners.



General mecanism of Het-Aryne coupling

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EMERGING THERAPIES FOR ACUTE MYELOID LEUKAEMIA USING hDHODH INHIBITORS ABLE TO RESTORE IN VITRO AND IN VIVO MYELOID DIFFERENTIATION

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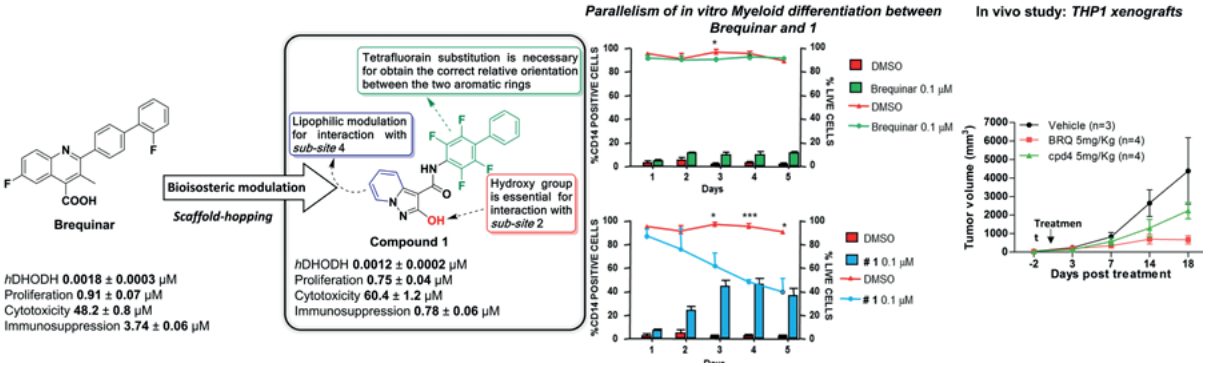
Bio(iso)steric replacement is a widely used approach in medicinal chemistry to improve the bioavailability, selectivity, potency and other properties of a lead compound. Since 2006, the authors have investigated hydroxylated heterocyclic systems, in order to create a sophisticate tool able to bioisosterically mimic the carboxylic and other acidic functions.(1) The application of this bioisosteric tool, that cover a wide range of p*K*a and chemiodiversity, led to new anticancer, antiparasitic, immunosuppressive and differentiating agents.Optimized chemical strategies for the synthesis of hydroxylated pentatomic heterocycles (substituted triazoles, pyrazoles, 1,2,5-oxadiazole, thiadiazole), as well as hydroxylated ring fused systems (pyrazolo[1,5-a]pyridine and benzoisoxazole) will be discussed, and each system analysed in terms of acidity and lipophilicity. The use of these systems in the modulation of acidic lead brequinar, led to a library of potent dihydroorotate dehydrogenase (DHODH) inhibitors.(2) DHODH is an emerging target for Acute Myeloid Leukaemia (AML), as myeloid differentiation can be obtained with DHODH inhibition.(3,4) Following that early affords, in this occasion we are presenting a new generation of inhibitors (Figure 1) able to reach the brequinar *h*DHODH potency levels.(5) Compound **1**, the best of two series, was found able to restore the myeloid differentiation in leukaemia cell lines (U937 and THP-1) at concentrations one digit lower than those achieved in experiments with brequinar. Moreover, a preliminary in vivo study of compound **1** on THP1 cells subcutaneous xenograft into the flank of NOD-SCID IL2rγnull (NSG) mice, shown an antileukemic activity reducing tumour volume if compared with control. Theoretical design, modeling, synthesis, SAR, X-ray crystallographic data, biological assays, Drug-Like proprieties, pharmacokinetic studies and *in vivo* evaluation on AML models are here presented and discussed.



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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF A NEW TRISUBSTITUTED PURINE DERIVATIVE AS SMOOTHENED ANTAGONISTS

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Since the Hedgehog (Hh) signaling pathway has been associated with cancer, it has emerged as a therapeutic target for cancer therapy.[1] The main target amongst the key Hedgehog proteins is the GPCR-like Smoothened (Smo) receptor. Therefore, some Smo antagonists that have entered clinical trials, including the FDA-approved drugs vismodegib and sonidegib, to treat basal cell carcinoma and medulloblastoma. However, early resistance these drugs, has spawned the need to find new, safer generations of Smo antagonists that avoid current clinical limitations.[6]

In this address, our work team has been designed and synthesized a series of trisubstituted purines and their antitumor activity was determined in a panel of cancer cell lines. Next, we performed a flow cytometry analysis of cell viability in some cell lines treated with the most promising compounds (selected according to their IC_{50} values and SI and compare with vismodegib). From these results, one hit compound (**4s**, **Figure 1**) was selected to evaluate its behavior as Smo antagonist. **4s** demonstrated, by qPCR on HT29 cells, that decrease Gli levels and by bodipy-cyclopamine assays, that is able to bind to Smo-WT with an IC50 value of 0.95 mM. A docking study indicates that **4s** bind at the same transmembrane pocket that vismodegib. In addition, a **4s**-loaded nanoemulsion (**4s**-NEM), showing that is highly effective in preventing post-surgery tumor reincidence and metastasis on *in vivo* basal cell carcinoma model.

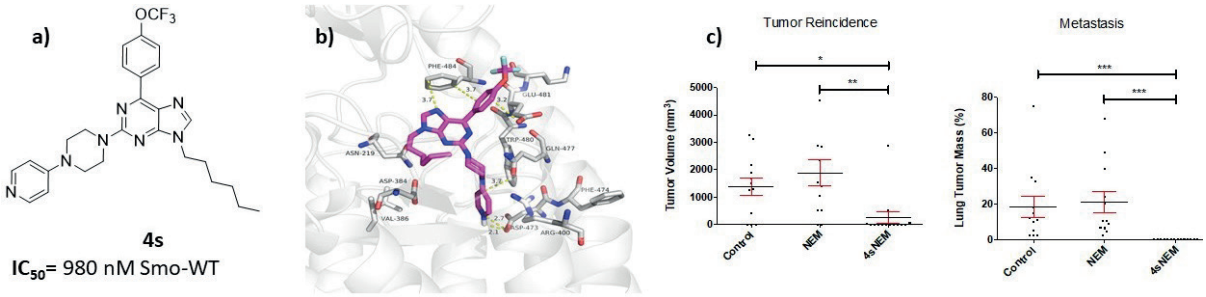

Figure 1. a) Chemical structures of **4s**; b) Molecular docking modes for **4s** at the Smo binding site; **c)** Tumour reincidence (left side) and metastasis (right side) employing a syngeneic C57BL/6 mouse model in presence of **4s-NEM**.

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VALORIZATION OF OLEUROPEIN VIA TUNABLE ACID-PROMOTED METHANOLYSIS

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Oleuropein is one of the major secoiridoids found in the olive leaf (0.5-2% (w/w) on dry basis).[1] Oleuropein structure can be divided in three subunits – glucoside, monoterpene and hydroxytyrosol (red, black and blue, respectively, Figure 1).[2] The monoterpene unit is a highly functionalized moiety that includes two esters, one alkene, one enol ether, one acetal and a stable chiral center at C-4. This multifunctional structure makes it difficult to be obtained by other means than extraction from natural sources.[3] In this context, we became interested in the valorization of oleuropein towards the synthesis of diverse and synthetically rich building blocks.

The acid-promoted methanolysis of oleuropein was studied using a variety of homogeneous and heterogeneous acid catalysts. Exclusive cleavage of the acetal bond between the glucoside and the monoterpene subunits or further hydrolysis of the hydroxytyrosol ester and subsequent intramolecular rearrangement were observed upon identification of the most efficient catalyst and experimental conditions. Furthermore, selected conditions were tested using Oleuropein under continuous flow and using a crude mixture extracted from olive leaves under batch. Formation of (-)-methyl elenolate was also observed in this study, which is a reported precursor for the synthesis of the antihypertensive drug (-)-ajmalicine.[4]

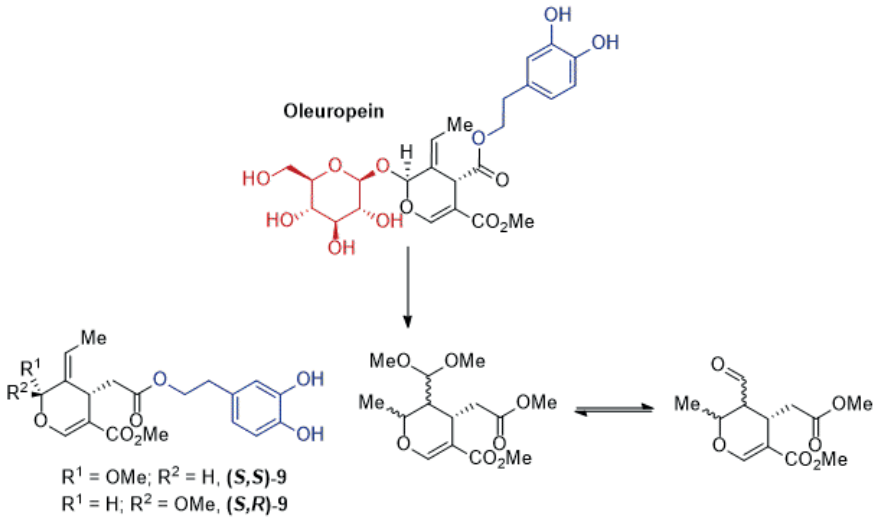

Figure 1. Tunable acid-promoted methanolysis of oleuropein.

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NOVEL BENZIMIDAZOLE DERIVATIVES AS MYELOPEROXIDASE INHIBITORS

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Neutrophils, the most abundant type of white blood cells in the organism, are responsible for defending the host against pathogens. As a part of their defense mechanism, they form phagosome in which pathogens are ingested and then killed by oxidative enzymes such as Myeloperoxidase (MPO)[1,2]. MPO is physiologically located in azurophilic granules of neutrophils and plays a significant role in antimicrobial system. After releasing into phagosome, it catalyzes the production of highly oxidative hypochlorous acids (HOCl) starting from hydrogen peroxide and chloride ions. HOCl damages the vital biomolecules of microorganisms and this damage results in antimicrobial activity. On the other hand, oxidative stress causes degranulation of neutrophils and MPO is poured into extracellular fluids generating HOCl that leads oxidation of biomolecules such as DNA, RNA, proteins, lipids of the host. MPO has been detected in glomerular basement membrane, atheromatous plaques, microglia, Alzheimer's and Parkinson patients' brains and. Taken together, all these pathological changes may result in renal injury, cardiovascular diseases, multiple sclerosis and neurodegenerative diseases[3,4]. As the understanding of the possible role of MPO/H_2O_2/Cl^- system on these diseases expanded, MPO have become an important therapeutic target.

Recently published data indicated that thiourea group and 5 membered fused rings such as indole, indazole and indazolone groups are commonly found in the structures of potential MPO inhibitors[5,6,7,8]. Based on these findings, we combined thiourea group and benzimidazole ring bearing different functional groups on the side chain. In this presentation, we will summarize the synthesis, MPO inhibitory activities and docking studies of the designed compounds.

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DISCOVERY OF NOVEL, DRUG-LIKE FERROPTOSIS INHIBITORS WITH IN VIVO EFFICACY

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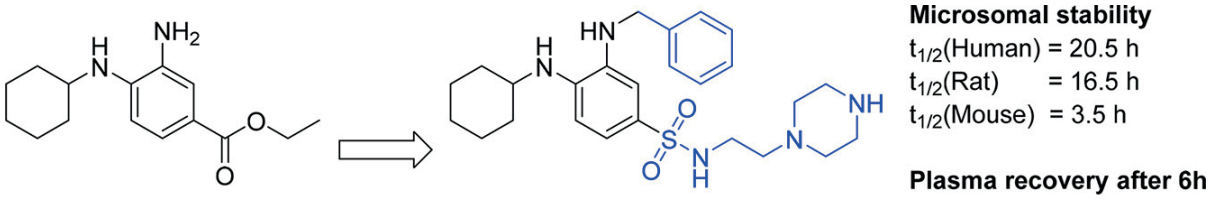
Nowadays, the field of cell death is facing new pathways: Ferroptosis is an iron-catalyzed, nonapoptotic form of regulated necrosis that results in oxidative lipid damage in cell membranes that can be inhibited by different class of molecules.[1] Between those, Ferrostatin-1 (Fer-1) emerged as a novel potent radical-trapping antioxidant (RTAs) suffered from solubility issues.[2] The reported study focused on the synthesis of a more stable and readily soluble series of Fer-1 analogues that potently inhibit ferroptosis enhancing the solubility.[3] The design of the new compounds starts from: 1) The replacement of the labile ester moiety with a sulfonamide to improve stability as well as potency. 2) The cyclohexyl moiety was deemed to be the most ideal substituent with regard to both potency and lipophilicity. 3) The introduction of an aromatic group on the 3-amino position greatly improved potency but also further decreased the solubility of the compounds

The most promising compounds, **UAMC-3234, UAMC-3206** and **UAMC-3203** showed a remarkable improvement in stability when compared to Fer-1 in the microsomal and plasma stability incubated with both human and rat microsomes. Compounds **UAMC-3234, UAMC-3206** and **UAMC-3203** also showed an improved protection compared to Fer-1 against multiorgan injury in mice and no toxicity was observed in mice after daily injection of **UAMC-3203** for 4 weeks. In silico study confirm the rapid insertion of **UAMC-3203** in a phospholipid bilayer, which aligns with the current understanding of the mechanism of action of these compounds.[4]

In conclusion, by introducing both a solubility improving group and a sulfonamide moiety to the Fer-1 scaffold, we were able to synthesize novel molecules that are more potent than Fer-1, while simultaneously improving solubility and stability.[5] These analogues have superior properties compared to Fer-1, showing in vivo efficacy, and represent novel lead compounds with therapeutic potential in relevant ferroptosis-driven disease models.



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A ZAFIRLUKAST-DERIVED DUAL FARNESOID X RECEPTOR/SOLUBLE EPOXIDE HYDROLASE MODULATOR

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The ligand-activated transcription factor farnesoid X receptor (FXR) acts as cellular bile acid sensor and is extensively studied as therapeutic target for the treatment of metabolic diseases, especially non-alcoholic steatohepatitis (NASH). FXR activation proved effective in reducing hepatic steatosis and fibrosis, and revealed anti-diabetic activity.[1] Soluble epoxide hydrolase (sEH) as a downstream enzyme in the CYP-pathway of the arachidonic acid cascade, converts epoxyeicosatrienoic acids (EETs) to the corresponding dihydroxyeicosatrienoic acids (DHETs).[2] Since EETs are anti-inflammatory lipid mediators, sEH inhibition constitutes an anti-inflammatory strategy that was repeatedly shown to have considerable potential in NASH treatment.[3,4] While FXR activation in NASH is mainly effective through metabolic effects and anti-steatotic activity[5], sEH inhibition has anti-inflammatory and anti-fibrotic effects in the liver.[6] Thus, combination of FXR activation and sEH inhibition may results in additive therapeutic efficacy in NASH.

To develop dual FXR activators/sEH inhibitors, we followed the approach of selective optimization of side-activities (SOSA).[7] We have identified the approved cysteinyl leukotriene receptor ($CysLT_1R$) antagonist Zafirlukast as a lead with moderate partial FXR agonism and sEH inhibiton. Initially, we addressed the sulfonamide and the urethane moiety of the lead Zafirlukast. Replacement of the 2-methylbenzenesulfonamide moiety and variation of the urethane moiety to residues derived from well-known FXR activators increased potency on FXR but simultaneously caused a decrease of inhibitory effects on sEH. However, with further minor structural modifications in the substitution pattern of the indole, we have developed a dual FXR agonist and sEH inhibitor with balanced potency on both targets.

High therapeutic potential of dual FXR/sEH modulators has already been demonstrated *in vitro* and *in vivo*.[5,8] Designed polypharmacological drugs with multiple modes of action appear to be especially promising in the treatment of the multifactorial disease NASH. For this reason, designed FXRa/sEHi hold great potential to improve future pharmacological NASH therapy.

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2-CARBAMOYLTHIENO[2,3-b]PYRIDINES CONSTITUTE A NEW CLASS OF ANTIPLASMODIAL AGENTS

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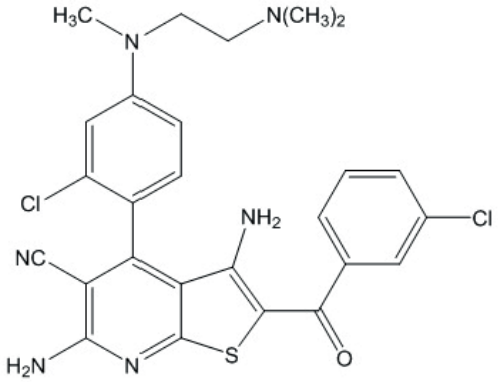
Despite impressive progress in prevention, diagnosis and treatment in recent years, malaria caused by the parasite *Plasmodium falciparum* is still one of the most prevalent and most dangerous infectious diseases worldwide[1]. Since recently cases of resistance against the well-established artemisinin therapeutics were reported, novel anti-malarial drugs are urgently required which differ from these standard drugs in structure and biological target. In a previous note we have reported 2-acylthieno[2,3-*b*]pyridines as inhibitors of the plasmodial enzyme *Pf*GSK-3 which display also antiplasmodial activity against erythrocyte stages of *P. falciparum* (e.g **1**: IC_{50} *Pf*GSK-3= 0.72 µM; EC_{50} *P. falciparum* = 1.2 µM)[2]. In an effort to improve the activity of these antiplasmodials, we have inserted an additional nitrogen atom into the side chain at 2-position, creating the related compound class of 2-carbamoylthieno[2,3-*b*]pyridines **2**. These compounds proved to be superior by means of antiplasmodial activity and displayed a considerable selectivity against human HEK293 cells. Interestingly, **2** were inactive as *Pf*GSK-3 inhibitors, a finding which casts doubt also on the biological target responsible for antiplasmodial activity of the ketone analogues like **1**. The paper will present the synthesis of **2** as well as data regarding enzyme inhibitory activity, antiplasmodial potency and cytotoxicity against HEK293 cells.



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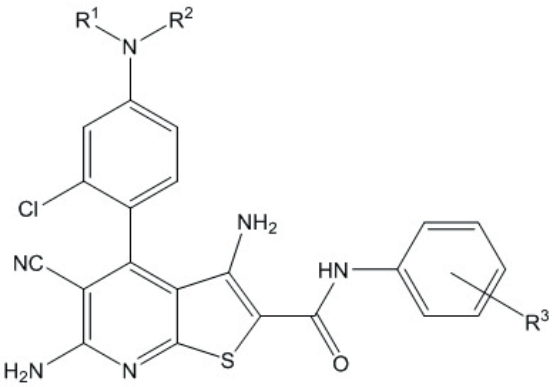

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Acknowledgements: Support by a stipend of the Evangelisches Studienwerk Villigst (to SIS) and by a fellowship from the Jürgen Manchot-Stiftung (to AA) is gratefully acknowledged.

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SMALL BUT SELECTIVE: DEVELOPING CHEMICAL PROBES FOR PKN/PRK2

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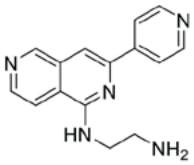
Chemical probes/tools help biologists answer mechanistic questions to validate disease pathways and new drug targets. They need not possess all the physiochemical properties of a drug-like molecule as these can been incorporated into a compound later in the drug discovery process. Chemical tools must be sufficiently stable, potent and selective against their given target protein.[1]

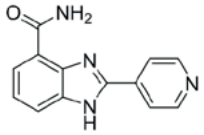
Collaborative efforts across academia and industry such as the Structural Genomics Consortium Human Kinase Chemical Probe Programme and PKIS/PKIS2 chemogenomic set[2] are currently undertaking the mammoth task of finding chemical probes for the 518 human protein kinases.

Protein kinase C-related kinase 2 (PKN/PRK2) is an AGC serine/threonine protein kinase. It is one of 3 homologues (PKN1-3) within the AGC kinase involved in a variety of pathways such as cytoskeleton regulation, transcription, migration and cell invasion. PKN2 is also a target of interest across several types of cancer. It currently does not have a selective chemical probe to help define its biological role.[3]

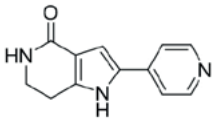
Three series of highly ligand efficient compounds selected from a ChEMBL screen (Fig. 1) have been developed and shown to bind potently to PKN2, with promising levels of selectivity against PKN1, and wider kinase panels. Their unusually small size challenges traditional criteria for drug-like compounds but can be utilised to design potent and selective molecular probes for PKN2 to help elucidate its role in disease.



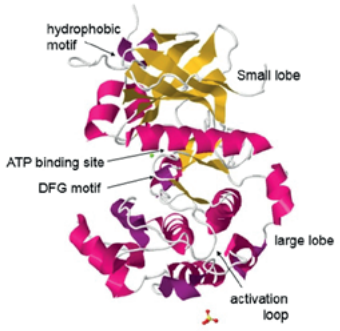
PRK2 IC_{50} 7 nm
J. Med. Chem., 2010,
53, 5400–5421



PRK2 K_i = 40 nM
J. Med. Chem., 2000,
43, 4084-4097



PRK2 K_i = 5 nM
J. Med. Chem., 2007,
50, 2647-2654



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SELECTIVE AND REVERSIBLE MODIFICATION OF KINASE CYSTEINES WITH CHLOROFLUOROACETAMIDES

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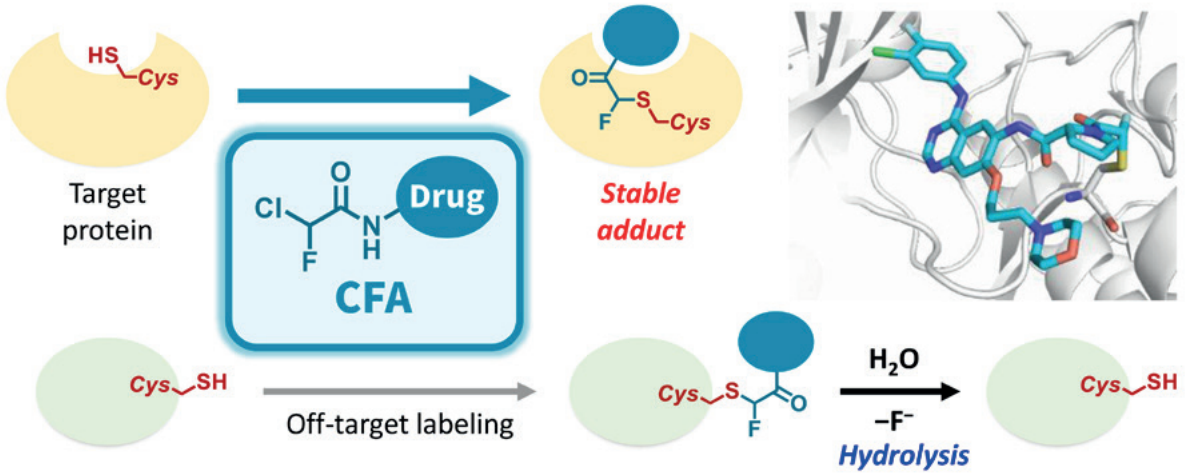
Irreversible inhibition of protein function with covalent inhibitors is a powerful approach for achieving increased and sustained pharmacological potency. Significant progress has been made in the last decade in the development of targeted covalent inhibitors (TCIs), especially for cancer-associated protein kinases. In the modern TCI design, acrylamide-type Michael acceptors are widely used as a chemically tuned reactive group (warhead) toward cysteine thiol. However, Michael acceptors have been reported to react with non-specific, off-target proteins in time- and concentration-dependent manner, which may result in dose-limiting toxicity[1]. Here, we introduce α-chlorofluoroacetamide (CFA) as a novel warhead of TCIs. Despite weak intrinsic reactivity, CFA-appended quinazoline showed high reactivity toward Cys797 of epidermal growth factor receptor (EGFR)[2]. In cells, CFA-quinazoline showed higher target specificity for EGFR than the corresponding Michael acceptors in a wide concentration range (0.1–10 μM). In addition, the cysteine adduct of the CFA derivative was susceptible to hydrolysis and reversibly yielded intact thiol but was stable in solvent-sequestered ATP-binding pocket of EGFR. This environment-dependent hydrolysis can potentially reduce off-target protein modification by CFA-based drugs. Oral administration of CFA quinazoline NS-062 significantly suppressed tumor growth in a mouse xenograft model. Furthermore, CFA-appended pyrazolopyrimidine irreversibly inhibited Bruton's tyrosine kinase with higher target specificity. These results demonstrate the utility of CFA as a new class of TCI warheads.



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SYNTHESIS OF ANTI-CANCER SESQUITERPENE VIA REGIO- AND DIASTEREOSELECTIVE [4 + 3] CYCLOADDITION

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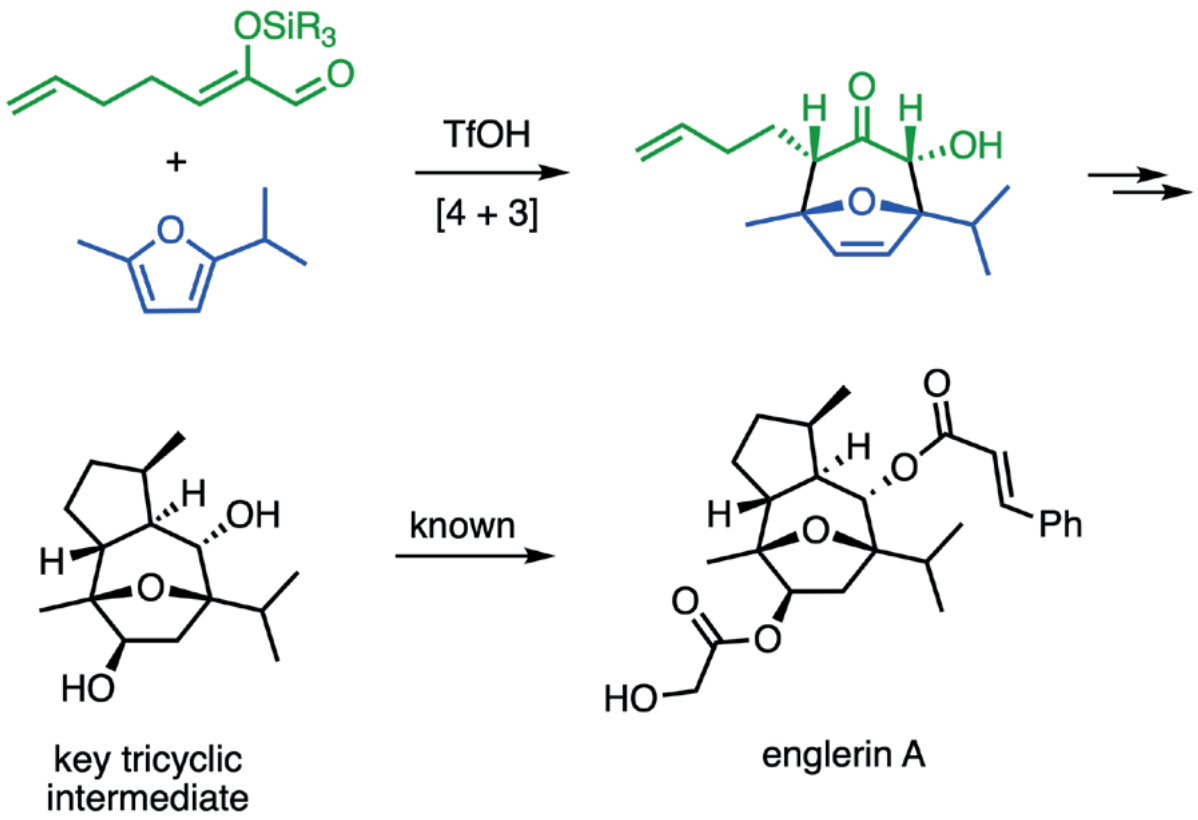
In 2009, Beutler and co-workers isolated englerin A (**1**) from the bark of *Phyllanthus engleri*, a plant of the Euphorbiacea family found in East Africa, particularly Tanzania and Zimbabwe, and **1** showed highly potent and selective growth inhibitory activities against renal cancer cell lines (GI_{50} 1–87 nM).[1] The guaiane sesquiterpene **1** has the unique tricyclic structure including 8-oxabicyclo[3.2.1]octane core. The characteristic structure and interesting biological properties of **1** attracted the attention of the synthetic chemistry community and about 20 research groups including Nicolaou and co-workers[2] reported the total and formal syntheses of englerin A (**1**) to date.[3]

In this presentation, we are going to present the formal synthesis of (±)-englerin A, including the preparation of the key tricyclic intermediate via acid-mediated regio- and diastereoselective [4 + 3] cycloaddition between the easily prepared formyl enol silyl ether and the 2,5-disubstituted furan.[4]



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IN VITRO AND IN OVO EVALUATION OF ROS-ACTIVATABLE ANTICANCER BORONATE PRODRUGS OF DOXORUBICIN

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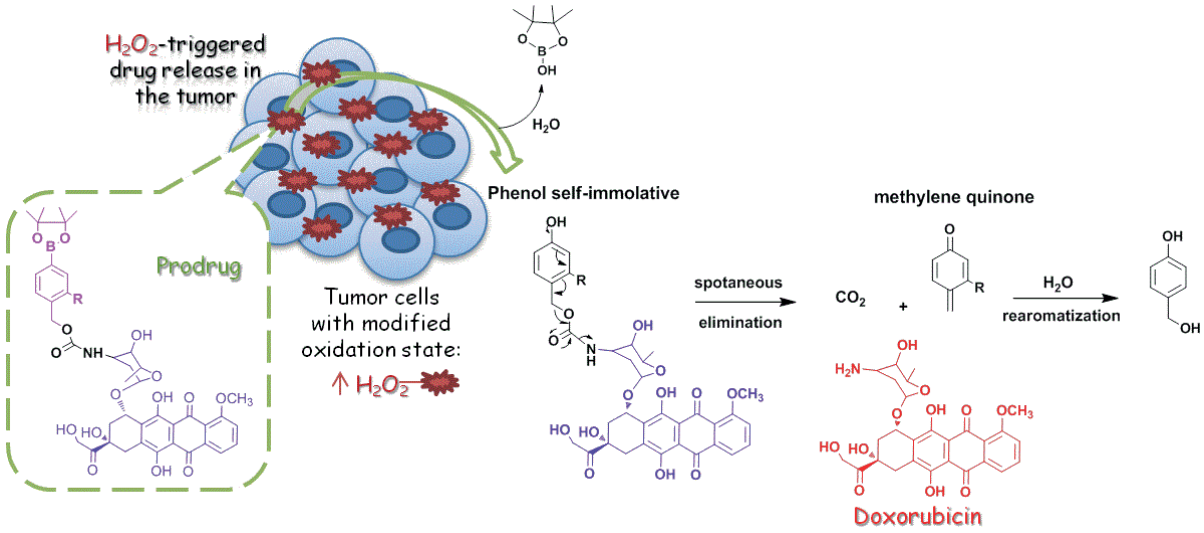
Pharmaceutical industries and public research centers have made oncology one of their priorities. Many drugs have been introduced on the market in order to treat cancer, however, many still suffer from a lack of selectivity for tumor cells over normal cells resulting in insufficient drug concentrations in tumors, systemic toxicity and appearance of drug-resistant tumor cells. To circumvent these drawbacks, a relevant strategy relying on the development of prodrugs designed to be activated after an enzymatic or a chemical reaction near the site of action has rose [1]. This strategy allows a specific release of the drug at its target site and could increase the therapeutic index of anticancer drugs. Among the different metabolic pathways, the activation by reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), appears particularly interesting and recent studies have shown that this property could be exploited for therapeutic benefits [2]. Arylboronates, in which the oxidation of the carbon-boron bond allows the formation of an electron donor alcohol group, act as quinone methide-based self-immolative spacers, leading to the release of the conjugated moiety after an electronic delocalization within the aromatic nucleus. As the cleavage of arylboronic acids and their ester derivatives takes place in presence of H_2O_2, we studied the design and development of new anticancer prodrugs consisting in the coupling of a pinacol boronate ester (trigger unit) to doxorubicin (active entity).



Scheme 1: Self-immolative mechanism of arylboronate-doxorubicin prodrugs.

On the basis of established structure-activity relationships[3], our study led to the design of a benzeneboronate profluorescent probe and three doxorubicin arylboronate prodrugs containing either, an unsubstituted bezenboronic acid, a fluorinated bezene homologue or a furan ring. The proof of concept of oxidation of the carbon-boron bound was investigated by adding increasing amounts of H_2O_2 to the profluorescent probe and by measuring the release kinetic of the fluorescent moiety. The capacity of cell line to produce ROS was also studied using the profluorescent probe. The in vitro evaluation of the designed doxorubicin prodrugs was investigated on a panel of cell line by determination of their IC_{50} value in comparison to doxorubicin. Finally, the efficacy of the most potent prodrug was evaluated in ovo on pancreatic cancer tumor model using the HET-CAM assay.

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METHIONINE INFLUENCE ON THE PROCESS OF OLIGOMERIZATION AND AGGREGATION OF SERUM AMYLOID A PROTEIN

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Serum amyloid A protein is defined as an acute phase protein because its increased production occurs as a response to injury and inflammation. As a result of high protein concentration in the body, it begins to aggregate and accumulate in various parenchymal organs. Amyloid deposits of the human SAA protein are dangerous because, through their size, they can disturb proper functioning of the affected tissues and organs.[1] It is important to understand the mechanism of SAA aggregation to find a way how to prevent the expansion of amyloidogenic processes.

The most amyloidogenic version of the human serum amyloid A protein, hSAA1.1, is a small protein consisting of one polypeptide chain with 104 amino acid residues. Its sequence begins with an arginine. The recombinant protein, rSAA1.1, is composed of 105 residues because it has a methionine as an additional residue at the *N* -terminus. In their native forms both proteins exhibit mainly an alpha helical structure, but they form with different rates a beta sheet structure from which fibrils are formed. The transmission electron microscopy shows different morphology of the aggregates of hSAA1.1 and rSAA1.1 and two mechanisms have been proposed for their formation.[2] The fact that one additional methionine residue significantly changes the properties of the protein is very intriguing, therefore we decided to study the aggregation process of both SAA variants and to check how the designed by us and intended as aggregation inhibitors short peptides will affect their fibrillization tendencies. In our research we used fluorescence and molecular filtration techniques.

Acknowledgments
This scientific work was financed under the program "Diamond Grant", as a research project DI2015 022445.

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DIFFERENTIAL ALLOSTERIC MODULATORY EFFECTS OF LITHOCHOLIC ACID ON PURINERGIC P2X RECEPTORS: INHIBITION OF P2X2 AND POTENTIATION OF P2X4 RECEPTOR

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Objectives: Purinergic P2X receptors (P2XRs) comprises seven subunits (P2X1-7) which are unevenly distributed in the central and peripheral nervous systems, immune system and endocrine system. Each of P2XR subunit consists of a large extracellular domain that contains ATP binding site, two transmembrane domains (TMs) and intracellular N- and C- termini. These regions offer multiple binding sites for positive or negative allosteric modulators enhancing or blocking receptor function. Endogenous allosteric modulators of P2XRs are divalent cations, phospholipids, neurosteroids and steroids. Here we tested a hypothesis that bile acids modulate function of P2XRs.

Methods and results: We tested several endogenously produced as well as synthetic bile acid derivatives in HEK293 cells expressing recombinant P2X2Rs and P2X4Rs, as well as in pituitary cells endogenously expressing P2XRs. We found that 5 of 28 bile acids tested exhibited inhibitory effect on P2X2R, but inhibition of P2X4R was never observed. Instead, the P2X4R was significantly potentiated by about 50 % of compounds (13/28), whereas significant potentiation of P2X2R was rarely observed (3/28). Electrophysiological recordings revealed that 10 μM lithocholic acid inhibited 1 μM ATP-stimulated P2X2 currents to 36±6 %, but potentiated 1 μM ATP-stimulated P2X4 currents to 296±27 %. Both inhibitory and stimulatory effects were concentration-dependent, threshold concentration was 0.3 μM. ATP concentration-response curve was shifted to the right for P2X2R, and to the left for P2X4R, indicating that lithocholic acid allosterically inhibited and potentiated receptor sensitivity to ATP, respectively. Isolithocholic acid also inhibited P2X2R, but potentiation of P2X4R was absent, indicating that inhibitory effect on P2X2 is not sterospecific, contrary to the potentiating effect on P2X4. Native P2X2R channels in identified pituitary gonadotrophs were also inhibited by lithocholic acid, whereas no potentiation was observed in these cells.

Conclusion: These results showed that lithocholic acid can be used as selective inhibitor of P2X2R in native cells simultaneously expressing several P2X subunits. Detailed knowledge about steroid modulatory site (s) is a prerequisite for development of new drugs against P2XR-based disorders.

Acknowledgment: *Supported by the Czech Science Foundation (grant 18-05413S), MEYS (the LQ1604 National Sustainability Program II, Project BIOCEV-FAR) and Grant RVO 61388963.*

SYNTHESIS OF CURCUMIN HETEROCYCLIC DERIVATIVES

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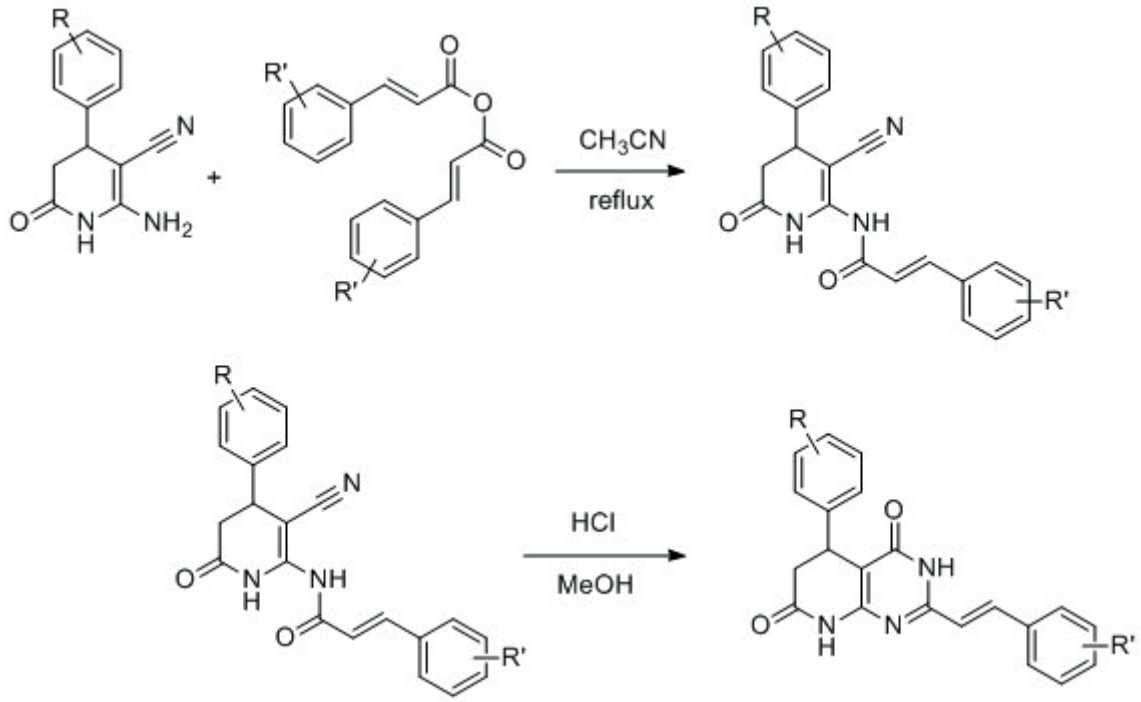
In the last decades curcumin has emerged as an important scientific topic due to its ability to act directly on more than 100 molecular targets (e.g., NF-κB, Nrf2, STAT-3, PPAR-γ) possessing a wide range of pharmacological activities, such as antibacterial, antifungal, antiviral, anti-HIV-1 integrase, anti-Alzheimer's, anti-Parkinson's, anti-arthritic, antioxidant, anti-inflammatory, and anticancer [1]. However, its poor solubility in water at acidic and physiological pH, fast metabolism, low bioavailability, the lack of specificity and the low potency of most of its actions call for analogs to be synthesized with increased potency and higher specificity. The 3,4-dihydropyridone was chosen as a scaffold to construct curcumin heterocyclic derivatives.



The 2-pyridones form structural units of many natural products and also possess interesting pharmacological properties such as reverse transcriptase inhibition of human immunodeficiency virus-1 (HIV-1), cardiotonic for the treatment of heart failure, antitumor, antibacterial, and other biological activities [2]. Coupled with curcumin these 3,4-dihydropyridone derivatives may provide even more diverse or enhanced pharmacological properties.

Acknowledgements: This study was supported by ERDF project No.1.1.1.2/VIAA/1/16/241 " Synthesis of Curcumin Heterocyclic Derivatives"

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PRODRUGS OF 6-DIAZO-5-OXO-L-NORLEUCINE (DON) WITH ENHANCED CSF DELIVERY IN MONKEYS AS A POTENTIAL TREATMENT FOR GLIOBLASTOMA

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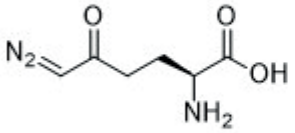
6-Diazo-5-oxo-*L*-norleucine (DON, **1**) is a non-standard amino acid, which was originally isolated from *Streptomyces* bacteria found in Peruvian soil in 1956. DON is one of very few naturally occurring diazoketones and it was characterized by Dion.[1] It has shown robust anticancer efficacy in preclinical and clinical studies, but development was halted by significant systemic toxicity. [2,3] To enhance DON's therapeutic index, we utilized a prodrug strategy to increase its brain delivery and limit systemic exposure. Several prodrugs were prepared and the most stable compound **2** was tested in monkeys, where it achieved 10-fold enhanced cerebrospinal fluid to plasma ratio versus DON.



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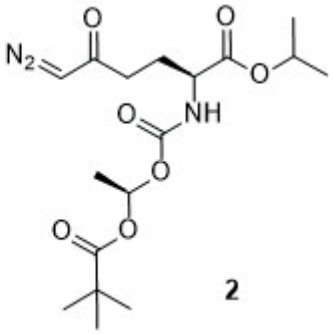

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SYNTHETIC AND MECHANISTIC STUDIES ON ONE-POT THREE-COMPONENT REACTIONS FOR THE SYNTHESIS OF 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES

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Multi-component domino reactions are efficient and effective methods in the sustainable and diversity-oriented synthesis of heterocycles. They provide the most powerful platforms to access diversity as well as complexity in a few reaction steps. The development of cheap, novel and green synthetic route for the synthesis of privileged heterocyclic scaffolds such as triazoles can be achieved using multi-component domino protocols. We are particularly interested in 1,2,3-triazoles, which are very important heterocycles in the field of chemistry and biology including polymer science, material science, bioconjugation, DNA-labeling supramolecular chemistry, and oligonucleotide synthesis. However, the synthetic routes toward more complex fully substituted 1,2,3-triazoles are still rare although the Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC),a representative process in click chemistry, has been known as a powerful tool for the synthesis of 1,2,3-triazoles, Herein, we report the one-pot three-component reactions for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles using alkyne, azide, base and an electrophile. The reaction conditions were exclusively investigated based on the plausible mechanistic aspects. Under the optimized conditions, the reactions proceeded smoothly and afforded the 1,4,5-trisubstituted 1,2,3-triazoles, which could be further converted into 1,2,3-triazole-fused bi-/tricyclic scaffolds. This multi-component reaction offered the most convenient, practical, and efficient route to useful polycyclic scaffolds in moderate to excellent yields.

NEW PHENOLIC CINNAMIC ACID DERIVATIVES AS SELECTIVE COX-2 INHIBITORS. CHEMISTRY AND STRUCTURE-ACTIVITY RELATIONSHIPS

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Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting cyclooxygenase (COX), of which there are two main isoenzymes, COX-1 and COX-2. The link between COX and inflammation has long been established, but it is now known that each isoenzyme contributes differently to that relation: while COX-1 is mostly associated with the synthesis of eicosanoids responsible for homeostatic physiological functions, COX-2 appears to be more closely related to inflammation responses in physiopathological processes. NSAIDs with no selectivity towards COX-2 therefore exhibit many side effects, especially on a gastrointestinal level. The search for NSAIDs with fewer side effects led to the development of drugs with a greater selectivity towards COX-2 instead of COX-1. While the incidence of gastrointestinal side effects has been reduced by these drugs, they have now been associated with cardiovascular complications such as heart attack, thrombosis and stroke. However, the need to find drugs with a greater selectivity towards COX-2 while avoiding harmful side effects remains, in order to treat diseases such as rheumatoid arthritis and osteoarthritis. In addition, selective inhibition of COX-2 has arisen as an interesting option for the treatment of colorectal cancer as well.

Following a number of studies with phenolic cinnamic acid derivatives, in which they have shown antioxidant, antitumoral and anti-inflammatory activities, hexylamides of several cinnamic acids were designed, synthesized and evaluated in order to assess their inhibitory activity towards COX-1 and COX-2. In this work, the chemistry of the prepared compounds is outlined (Figure 1) and structure-activity relationships were established, revealing that phenolic hydroxyl groups play a key role in the inhibition of both COX isoforms, while the presence of di-*tert*-butyl groups in the phenyl ring appears to be strongly related to selective COX-2 inhibition. Some of the studied compounds exhibited a remarkable selectivity towards COX-2, which means that they could be further studied in order to develop new effective anti-inflammatory drugs with a better safety profile.

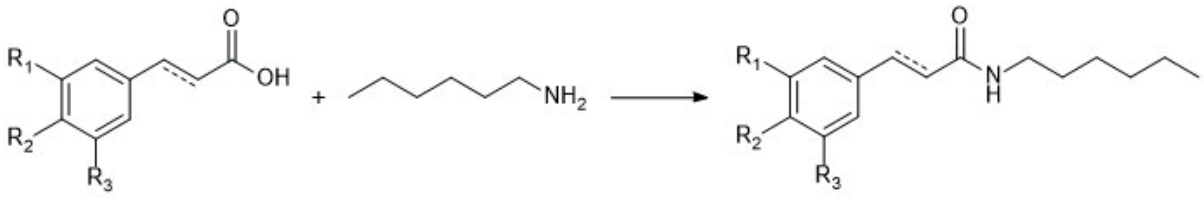

Figure 1

COMPUTATIONAL STUDIES OF NADP(+)-DEPENDENT MITOCHONDRIAL MALIC ENZYME 2, A POTENTIAL DRUG TARGET FOR CANCER

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Cancer is the second leading cause of death globally and is estimated to account for 9.6 million death in 2018. The main goals of treatment programs are to cure or considerably prolong the life of patients and to ensure the best possible quality of life for cancer survivors [1]. Currently, there is rising contemplation on Krebs cycle enzymes as potential chemotherapeutic hits due to their affiliation with tumour metabolism. The NADP(+)-dependent mitochondrial malic enzyme 2 (ME2) has been studied due to its function as a provider of pyruvate and reducing power to the cell for the biosynthesis of fatty acids and nucleotides along with maintenance of redox balance. Multiple lines of evidences, including ME2 overexpression on tumour cell lines indicates it is a therapeutic target for cancer chemotherapy [2]. In this work, computational studies were performed in order to gain structural insights into allosteric activation/inactivation on ME2. Principal Component Analysis (PCA) and Normal Mode Analysis (NMA) were performed to explore the main dynamics of the protein structures available in PDB, using ProDy software [3]. Comparison of PCA results with the NMs through an overlap metric showed that the biggest conformational variation present on the available structures (PC1) has a good overlap (~65%) with the mode 10, PC2 has an overlap of ~50% with mode 4 and PC3 an overlap of ~70% with mode 1. Mode 1 represents a dimer-twisting motion, mode 4 shows a distancing of the C-domains, and mode 10 a rotation of those C-domains. Calculating the vector that explains the transition between two conformational states, and performing the overlap metric with some predicted modes, it was possible to detect which of those modes are responsible for the studied conformational change. The presence of malate+fumarate+Mg creates a conformational change that affects mainly mode 10; the presence only of Lu3+, affects mainly mode 4 and the presence of an inhibitor on the active site seems to affect mainly the motion represented by mode 1. Altogether, these data suggest that ME2 activation is mainly related to conformational changes represented by mode 10, the C-domain rotation. The study of the residues involved in this motion will help the development of ME2 inhibitors, considering not only drug-receptor interactions but also their ability to stimulate this conformational change in the enzyme.

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RISK ASSESSMENT OF CANNABINOIDS DEGRADATION PRODUCTS USING IN SILICO APPROACH

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The most abundant cannabinoids present in the *Cannabis* plant are Δ9-tetrahydrocannabinol (THC), the main psychoactive compound, and cannabidiol (CBD) [1]. CBD was the first FDA approved drug from *Cannabis* plants for the treatment of seizures associated with rare syndromes, without psychotropic effects and abuse liability [2,3]. The degradation product of THC, cannabidinol (CBN) does not occur naturally in the plant and acts as sedative and anticonvulsant that is anti-inflammatory [4]. According to the International Conference on Harmonization (ICH), it is of fundamental importance that the mechanisms governing degradation of newly developed long-term use drugs are well understood. It is also essential that the identity of the degradation products (DPs) and their potential toxicities are characterized [5]. In this context, the goal of this study was to evaluate the potential toxicities of degradation products of the most common cannabinoid presented in cannabis strains: cannabidiol (CBD) and cannabinol (CBD) employing *in silico* techniques. Considering stress testing, the predictions of DPs resulted in a total of 26 and 7 DPs for CBD and CBD, respectively. *In silico* risk assessment were obtained using ADMET predictor® and indicated that: (1) all CBD_DPs (1-26) and CBN_DP3, CBN_DP4, CBN_DP5, CBN_DP6 and CBN_DP7 were predicted with hepatotoxicity risk, since these DPs presented a potential in elevating serum levels of liver enzymes used in the diagnosis of liver injury; (2) mutagenicity was predicted for CBN_DP3 e CBN_DP4, based on Ames test; (3) hERG inhibition, an indicative of cardiotoxicity, was predicted for CBN_DP5, CBN_DP6 and CBN_DP7; (4) acute toxicity in rats was predicted for all CBD_DPs (1-26) and CBN_DP5, CBN_DP6 e CBN_DP7, since these DPs presented LD50 < 300mg/kg and (5) all CBD_DPs (1-26) and CBN_DPs (1-7) were predicted with reproductive toxicity, since they may be related to anything that disturbs the reproductive process of organisms, including adverse effects to sexual organs, behaviour, ease of conception, and developmental toxicity of offspring both before and after birth (6) carcinogenicity, an important analysis for prediction of cancer induction, was assigned to CBD_DPs (1-26) and CBN_DPs (5-7).

SELECTIVE TOLL-LIKE RECEPTOR 7 AGONISTS WITH NOVEL CHROMENOIMIDAZOLONE, QUINOLINE AND QUINAZOLINE SCAFFOLDS

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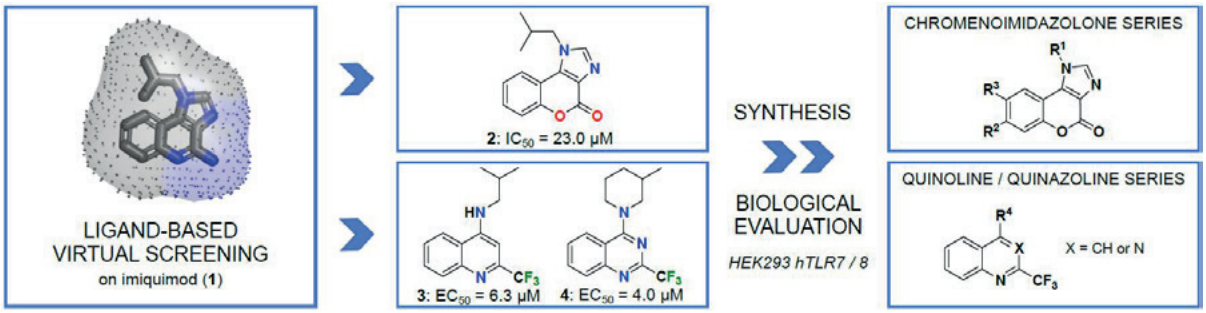
Toll-like receptors (TLRs) are pattern-recognition receptors that are involved in host cell recognition and initiation of immune responses against bacteria, viruses, fungi, and parasites [1]. To date, 10 functional TLRs have been identified in human. TLR7 and TLR8 specifically recognize single-stranded RNAs, and have thus been considered as emerging therapeutic targets for several life-threatening diseases, such as viral infections, autoimmune diseases, and cancers [1, 2].

Two different ligand-based virtual screening protocols with imiquimod (**1**) as a query compound were used for identification of novel TLR7 ligands [3, 4]. The first hit compound was 1-isobutylchromeno[3,4-d]imidazol-4(1H)-one (**2**) which showed potent TLR7 antagonist activity [3]. Thus, we explored the chemical space around the chromenoimidazolone scaffold and synthesized selected analogs to obtain key information about structure–activity relationships of chromenoimidazolone-based TLR7 modulators [4]. For discovery of novel scaffolds from the second series, our in-house ligand-based virtual screening protocol, known as LiSiCA, was used. The high-ranked hit compounds that were topologically most similar to the reference compound **1** were 2-(trifluoromethyl)quinoline/ quinazoline derivatives **3** and **4**, which were further used as scaffolds for preparation of the second series of novel TLR7 agonists [4]. Synthesis of a focused library of analogs, biological evaluation on HEK293-hTLR7/8 cells, and docking studies provided systematic exploration of structure–activity relationships indicating that a secondary or tertiary amine with smaller flexible alkyl substituents or bulkier rigid aliphatic rings as R^4 on 2-(trifluoromethyl)quinoline/ quinazoline scaffold is required for potent TLR7 agonist activity [4]. Our study demonstrates successful *in-silico* discovery of novel TLR7 versus TLR8-selective compounds as promising chemical probes for further development of potent small-molecule immunomodulators.



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RATIONAL DESIGN OF NOVEL TOLL-LIKE RECEPTOR 8 LIGANDS

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Toll-like receptors (TLRs) play a central role in innate immunity by recognizing invading pathogens and host-derived danger signals, and initiating the inflammatory response.[1] Aberrant TLR response is involved in the pathogenesis of multitude of severe diseases and TLRs therefore represent attractive targets for novel therapeutic agents.[2] TLR8 agonists show potential therapeutic applications in diseases like cancer, allergic rhinitis or as vaccine adjuvants. On the other hand, TLR8 antagonist could be beneficial to treat autoimmune diseases.[3] The research aim of this project is to discover and pharmacologically characterize novel small molecule TLR8 ligands.

In the initial phase of the project, structure-based 3D pharmacophores were created from agonist bound crystal structures of TLR8 ectodomain available from the Protein Data Bank (PDB) using LigandScout.[4] The most representative pharmacophores were used to screen databases of 5 million commercially available drug-like compounds. After a careful visual inspection, nine most promising compounds were selected for experimental validation based on their predicted docking poses, diversity and availability. Analogs of active compound were identified using a shape based tool ROCS.[5] In order to understand SAR, we used molecular docking and molecular dynamics simulations to investigate possible binding modes.

Three pyrimidine-based compounds show inhibitory activity in HEK293 cells overexpressing hTLR8 in the presence of the TLR8 agonist CL075. Compounds neither cause cellular toxicity nor inhibition of TLR signaling induced by other TLR subtypes. Furthermore, compounds potently reduced CL075-induced IL-8 and TNF secretion in THP-1 macrophages.

Conclusively, we have identified novel and promising TLR8 inhibitors *in silico* and confirmed biological activity, selectivity and low cytotoxicity *in vitro*.[6]

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DESIGN AND SYNTHESIS OF NEW SQ109 DERIVATIVES AGAINST TUBERCULOSIS AND OTHER INFECTIONS

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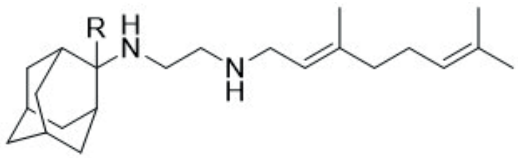
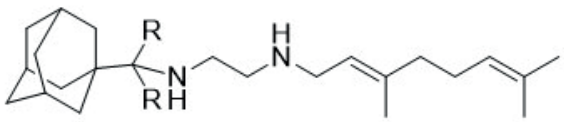
Despite the introduction of an effective treatment 40 years ago, tuberculosis (TB) is spreading globally. Over the past 10 years, recent efforts from various groups have generated a promising TB drug pipeline [1]. SQ109 (N-geranyl-N-(2-adamantyl)ethane-1,2-diamine) proved to be more active than ethambutol both in vitro and in vivo and has more favorable pharmacokinetic properties and, importantly, has been shown to accumulate in the lung, the site of M. tuberculosis infection. SQ109 proved to be active against both drug-susceptible (MIC ranging from 0.2 to 0.39 mg/mL) and drug-resistance (MIC ranging from 0.2 to 0.78 mg/mL) M. tuberculosis strains in vitro and clinical isolates of M. tuberculosis [2-4]. SQ109 showed a distinctive pharmacological profile in mice, while it showed poor oral bioavailability in rats and dogs. In both single and multi-dose Phase I and Phase II clinical trials, SQ109 proved to be both safe and well- tolerated [2-4].



SQ109: R=H
AK116: R=Me
AK118: R=Pr



AK117: R=Me
AK119: R=Et

Recently an x-ray structure of SQ109 in complex with MmpL3 provided a platform for structure-based drug design [5]. Using the MmpL3-SQ109 structure we designed and synthesized new analogues as a part of an ongoing project to develop highly potent anti-tuberculosis therapeutics, with SQ109 being optimized.

To achieve these analogues of SQ109, geranylamine was synthesized from the low cost geraniol. The desired aminoadamantane conjugates were obtained through a mild reduction, applied for the first time in these derivatives. The derivatives are under testing against Trypanosoma brucei, Mycobacterium smegmatis and TB and the currently obtained results showed that the derivatives are 10-fold more potent than SQ109 against T. brucei and M. smegmatis.

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FLUORESCENT MACROLIDE PROBES FOR EXAMINATION OF ANTIBIOTIC RESISTANCE

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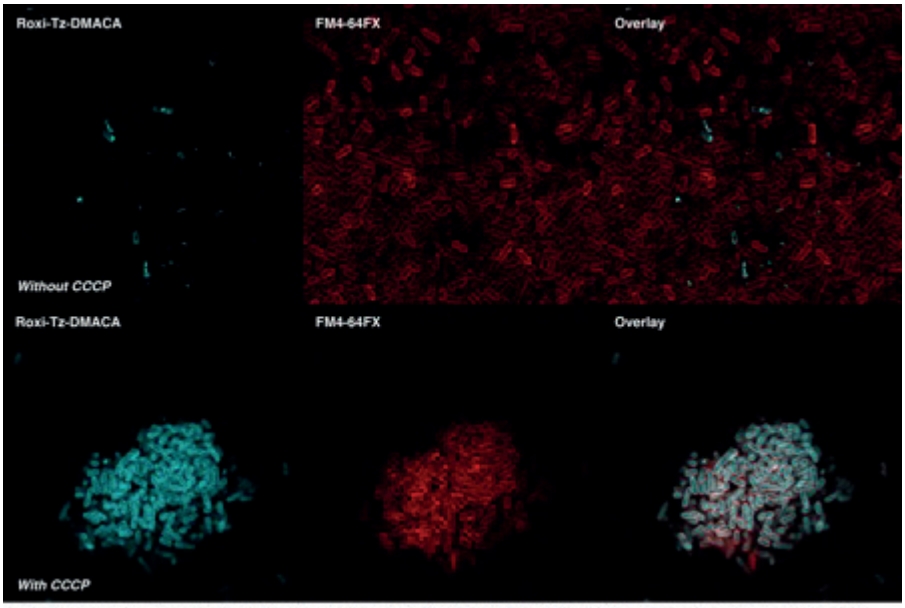
The emerging crisis of antibiotic resistance requires a multi-pronged approach in order to avert the onset of a post-antibiotic age. One critical aspect is studying modes of resistance, including efflux pump upregulation, drug degradation, and substrate mutation. To enable this work, functional tools are required, and one class which has been gaining momentum in recent years is fluorescent antibiotics. To this end, several fluorescent derivatives of erythromycin have been synthesised via a central azide intermediate. These analogues retain the same pattern of antibiotic activity as the parent drug, and are capable of labelling both Gram-positive and -negative bacteria for microscopy. Super-resolution live cell confocal microscopy revealed internal localisation for the Roxi-Tz-DMACA probe, whilst the NBD probe appeared membrane associated due to the increase in fluorescence in lipid environments. By using a mar1 mutant *Escherichia coli*, it could be shown that internalisation of the DMACA probe was vastly increased upon addition of efflux pump inhibitor CCCP. This phenomenon could be observed both using confocal microscopy and analysis of cell contents post lysis. In summation, fluorescent probes based on erythromycin have successfully synthesised and shown to have utility in studying antibiotic resistance, including efflux pump activity.



Confocal microscopic images of live AG102 *E. coli* cells stained with Roxi-Tz-DMACA and FM4-64FX (membrane dye) with and without CCCP

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DESIGN, SYNTHESIS AND BIOCHEMICAL EVALUATION OF NOVEL PYRIDINE ANALOGUES WITH c-SRC KINASE INHIBITORY ACTIVITY

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Tyrosine kinases have been associated with oncogenic transformation and represent the target of less toxic anti-tumor treatments. Among the many tyrosine kinases, Src is a fundamental enzyme for cell differentiation, replication, growth, adhesion, motility, angiogenesis and bone metabolism being involved in transmitting extracellular signals across the cell membrane to distant locations in the cytoplasm and in the nucleus. Src family kinases (SFKs) are categorized into nine groups sharing the similar structure and functions: c-Src (cellular Src), Yes, Fyn, Lyn, Lck, Hck, Fgr, Blk and Yrk. Especially, cellular Src (c-Src) kinases play a critical role in cell adhesion, proliferation, angiogenesis and cancer. Many studies exhibit that c-Src could be an appropriate target for the pharmacological treatment of cancers, skeletal metastases and different kind of diseases. As expected, the c-Src inhibitors demonstrated efficaciously to reduce bone metastases, neuroblastoma, and cystic fibrosis in preclinical studies. These results have initiated the development of innovative therapies for the treatment of fibrosis disease. In this study, several pyridine derivatives have been designed, synthesized and evaluated for their inhibitory potency towards the tyrosine kinase c-Src. The rational design and synthesis of a series of pyridine analogues will be presented and an SAR analysis will be discussed. All data will guide the further optimization of c-Src inhibitors toward more potent agents.

MULTI-COMPONENT REACTIONS: A BEAUTIFUL DEVELOPMENT OF COVALENT INHIBITORS

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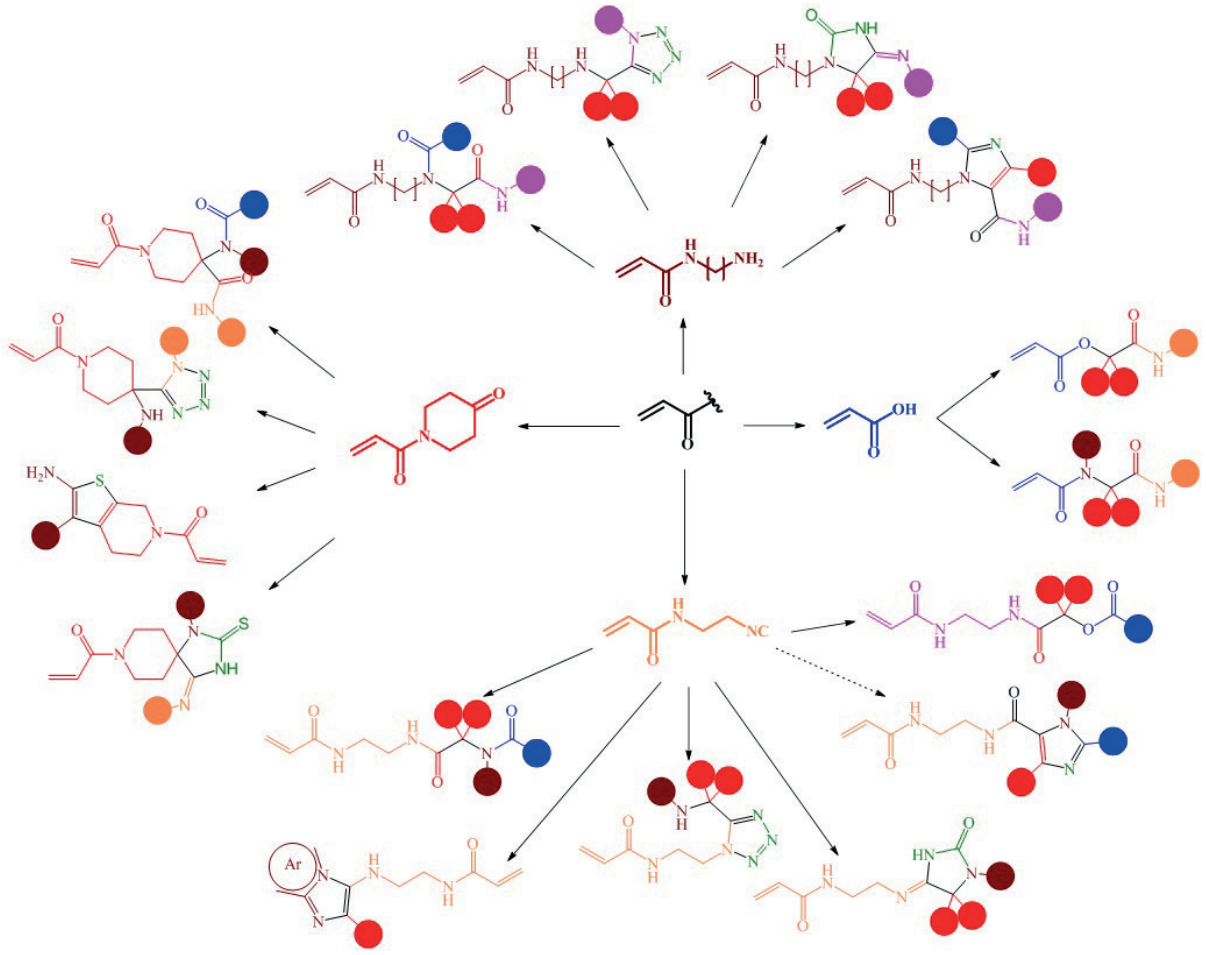
Covalent inhibitors play important role in drug discovery and therapeutics. About 30% of marketed drugs are covalent inhibitors, ranging from obesity to cancer.[1] The toxicity of covalent inhibitors is a major concern, but the advantages provided by them offer a large opportunity of exploring them even further. There are different warheads that act as covalent inhibitors, for example α,β-unsaturated carbonyl, epoxide, β-lactam, β-lactone, halomethyl, α-keto derivatives, etc.[2] Multi-component reactions are powerful tools which can be explored to synthesize covalent inhibitors. This work focused on synthesizing α,β-unsaturated carbonyl compounds, a Michael acceptor that binds covalently towards cysteine residue, through multi-component reactions.



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MULTICOMPONENT REACTION BASED SYNTHESIS OF 1-TETRAZOLYLIMIDAZO[1,5-a]PYRIDINES

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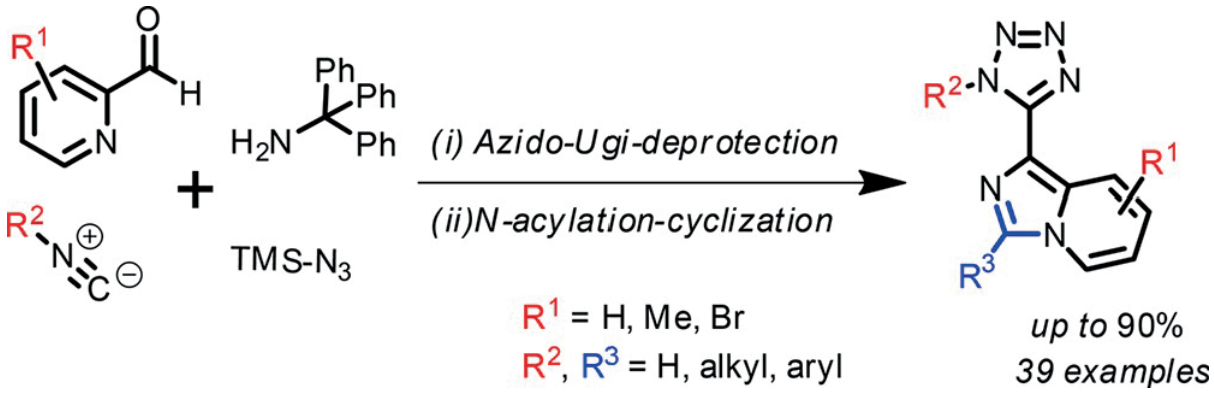
A series of unprecedented tetrazole-linked imidazo[1,5-a]pyridines are synthesized from simple and readily available building blocks. The reaction sequence involves an azido-Ugi-deprotection reaction followed by an acetic anhydride-mediated *N*-acylation-cyclization process to afford the target heterocycle. Furthermore, the scope of the methodology was extended to diverse R_3 substitutions-by employing commercial anhydrides, acid chlorides, and acids as an acyl component. The scope for the postmodification reactions are explored and the usefulness of the synthesis is exemplified by an improved three-step synthesis of a guanylate cyclase stimulator.



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DESIGNING SMALL MOLECULE PEPTIDOMIMETICS FOR THE THROMBOPOIETIN RECEPTOR

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Primary Myeloid fibrosis (PMF) is characterized by a structural remodeling of the bone marrow which is replaced with a fibrous scar-like material that greatly affects the production of red, white blood cells and platelets. It is further associated as a hematopoietic stem cell (HSC) disorder which leads to progressive organomegaly, anemia and a leukoerythroblastic peripheral blood picture. It also has the potential to evolve to acute leukemia.[1] There are currently no viable treatments for this disorder, except for HSC transplantation, which comes with considerable risks. Thrombopoietin is an important cytokine required for platelet production and HSC maintenance. It binds to the c-MPL receptor, which activates the JAK-STAT signaling pathway.[2] Our group has designed the first small 20-amino acid peptide which acts as an antagonist at this receptor and is a potential new approach for the treatment of PMF.[3] Our current research aim is to develop a small molecule mimic utilizing computational modeling and a high-throughput screening approach.

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STRUCTURAL MODIFICATIONS AND PHARMACOLOGICAL EVALUATION OF 4-PYRIDYLPIPERAZINE DERIVATIVES AS ACTIVE AND SELECTIVE HISTAMINE H3 RECEPTOR LIGANDS

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Histamine H_3 receptors (H_3R) are constitutively active G-protein coupled receptors (GPCR) mostly expressed in CNS that serve as histamine (among other neurotransmitters) brain levels modulators. Therefore, their blockade might provide useful pharmacological target for treatment of many CNS-based diseases such as narcolepsy, schizophrenia, Alzheimer´s and Parkinson's diseases, obesity, and attention-deficit hyperactivity disorder (ADHD) [1], also as dual or multiple acting ligands [2].

Undoubtedly, the replacement of native imidazole ring with other heterocyclic moieties was a milestone in the search for new histamine H_3R ligands, in terms of (bio)activity and possible side effects reduction. One of such replacement is the piperazine moiety - a significant versatile chemical scaffold in rational drug design for numerous GPCR ligands.

Based on our research results hitherto, 4-pyridylpiperazine moiety in the basic part of the compound determines their high affinity at and selectivity for human H_3R. Such position of the nitrogen atom in an aromatic ring attached to piperazine moiety has turned out to be a key structural element for suitable interaction with its biological target [3]. In order to determine the "eastern part" substituents of the molecule, structural modifications of previously obtained compounds including replacement of branched alkyl benzene substituents, with bulky aromatic groups were undertaken. Moreover, subsequent extension of alkyl linker up to eight methylene groups was also performed. Considering structural similarity of our compounds to other GPCR ligands, profiling of affinity at histamine H_1, dopamine D_2 and adrenergic α_1 receptors was also carried out.

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LIPOPHILIC GUANIDINE DERIVATIVES OF THE GLYCOPEPTIDE ANTIBIOTIC TEICOPLANIN - SYNTHESIS AND IN VITRO ANTIBACTERIAL EVALUATION

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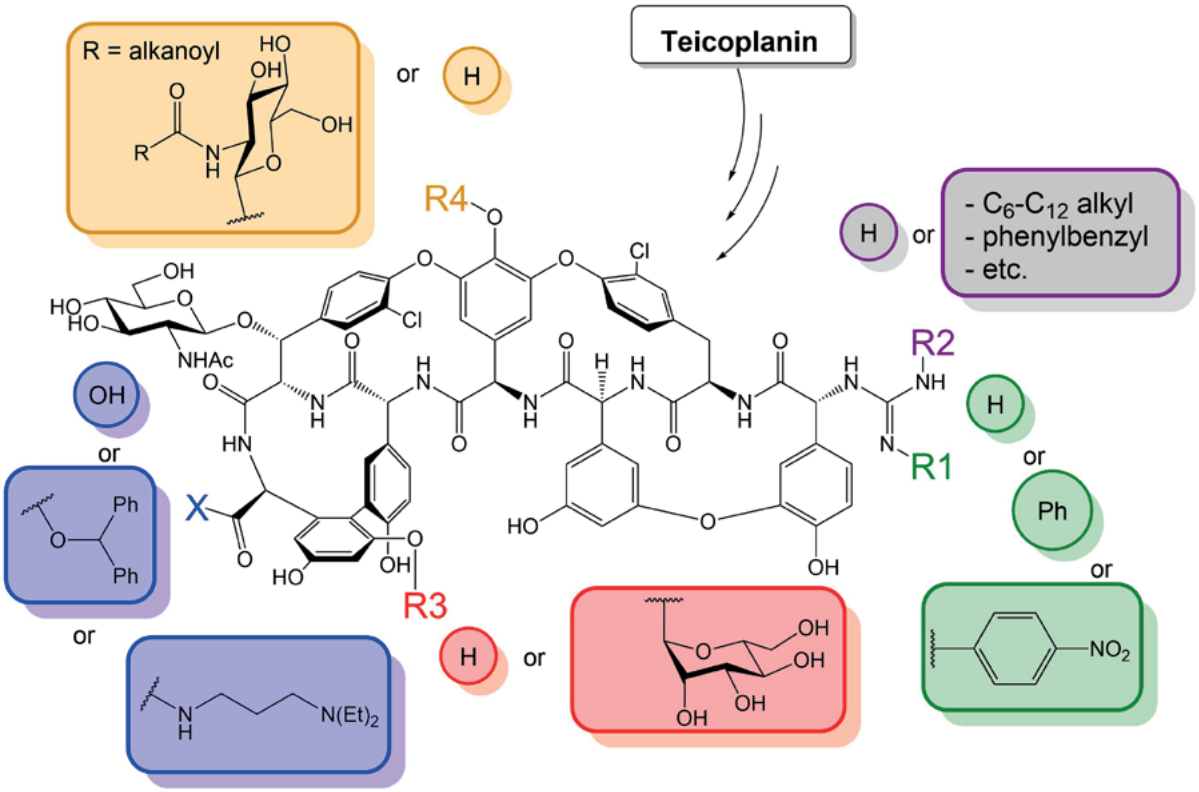
The resistance to antibiotics is a global phenomenon with a serious negative impact on public health. One of the common nosocomial pathogenic bacteria are vancomycin resistant enterococci (VRE), namely *E. faecalis* and *E. faecium.* This resulted in the development of the second generation of glycopeptide antibiotics - lipoglycopeptides - which are able to eradicate VRE strains effectively. The attachment of lipophilic moieties to the parent molecules is a well-known and widely utilized method for obtaining compounds with enhanced antibacterial activity due to the resulting additional mechanisms of action. Our research group has been working on the synthesis of new glycopeptide derivatives for several years, mainly focusing on the *N*-terminal transformations of the naturally occurring glycopeptides. Our modifications of teicoplanin has yielded compounds with excellent in vitro antibacterial activity in multiple cases. One of our recent results is the synthesis of *N*-terminal guanidine derivatives of teicoplanin and one of its pseudoaglycons (TA_3-2) preferentially using disubstituted carbodiimides. This modification was carried out after the prior protection of the *C*-terminal carboxyl group. We have also prepared the unsubstituted guanidine derivative of TA_3-2. The in vitro antibacterial activity of 18 new compounds was evaluated against a standard panel of Gram-positive bacteria. Based on the results, several of the compounds have excellent in vitro activity both against teicoplanin resistant staphylococci and enterococci.



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STRENGTHENING HELICITY OF OLIGO-PEPTOIDS THROUGH A SYNERGY EFFECT BETWEEN CHIRAL AND ACHIRAL SIDE CHAINS

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Peptoids (*N*-substituted glycine oligomers) are an important class of foldamers capable of adopting a range of unique secondary structures based on the cis/trans geometries of their constituting main chain tertiary amide bonds.[1] Structural versatility of peptoids is also driven by the capacity of sequence-specific polypeptoids to form supramolecular assembly including bilayer nanosheets.[2] Examples of reported secondary structures for linear peptoids are the PolyProline-type I (PPI) and II helices,[3] the ribbon structure,[4] the peptoid square helix (η-helix),[5] and a zigzag pattern called ('sigma')-strand.[6] Since their backbones lack free NH amides, the capacity to form well-ordered structures is strictly related to the nature of the side chains, upon which the cis/trans peptoid amide equilibrium depends. In a recent past, great efforts have been devoted to controlling peptoid amide bond geometries through noncovalent interactions to minimize backbone conformational heterogeneity. For example, the bulky naphthylethyl (1npe)[7] and *tert*butylethyl (1tbe)[8] α-chiral side chains, or the achiral *t*Bu[9] promote cis-amides and were used to generate stable all-cis PPI peptoid helices. We will report here on the synthesis and conformational study of oligopeptoids incorporating various proportions of site-specific chiral and achiral aliphatic *cis*-inducing side chains. The synthetic challenge of preparing conformationally homogeneous and robust PPI helical peptoids with site-specific functionalised side chains will be also addressed.

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ATOM TRANSFER RADICAL ADDITION OF A-BORYL CARBON-CENTRED RADICALS TO ALKENES FOR A NEW CYCLOPROPANATION REACTION

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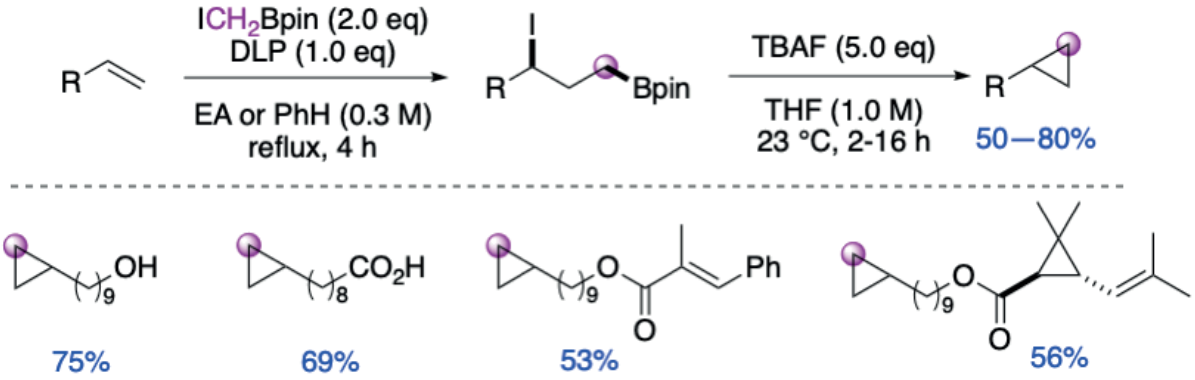
The vacant boron p-orbital in organoboranes has a stabilizing influence on a radical formally located on an adjacent carbon atom.[1,2] Boronic esters, with two sets of oxygen lone pairs partially delocalized into the B p-orbital, reduce the electrophilicity and stability of the radical.[3] Nonetheless, we focused our attention on a moisture- and air-stable C_1-carbene-like-synthon/ radical precursor, which lead us to thehitherto underexplored yet commercially available ICH_2Bpin.[4–6] The resulting g-iodoboronic esters are infrequently found in the literature despite containing two proximal and orthogonally transformable carbon–heteroatom bonds.



The investigation concluded with an operationally simple, one-pot protocol to affect an atom transfer radical addition (ATRA) of ICH_2Bpin over an alkene telescoped with a subsequent nucleophilic treatment to trigger a 1,3-cyclization. The radical is selective for unactivated, terminal alkenes in the presence internal electron-rich or electron-poor olefins. To generate the radical we do not need any metal, may use benign and accessible reagents and solvents, can work on multi-gram scales, and tolerate a wide range of functional groups. Full details of the chemoselectivity and complementarity of this cyclopropanation in comparison to other methods will be discussed in more detail.

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TUMOR-TARGETED DELIVERY OF 6-DIAZO-5-OXO-L-NORLEUCINE (DON) USING SUBSTITUTED ACETYLATED LYSINE PRODRUGS

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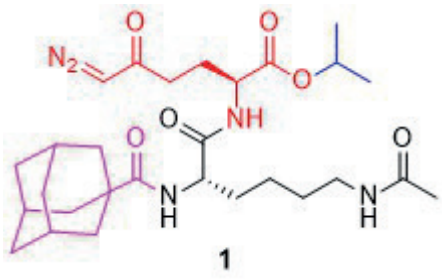
6-Diazo-5-oxo-L-norleucine (DON) is a glutamine antagonist with robust anticancer efficacy, yet its therapeutic potential was hampered by its biodistribution and toxicity to normal tissues, specifically gastrointestinal tissues which are highly glutamine-dependent. DON acts as an irreversible inhibitor of many glutamine utilizing enzymes critical for the synthesis of nucleic acids/ proteins and the generation of α-ketoglutarate for energy metabolism. The anticancer and autoimmune activities of DON has been shown repeatedly in both preclinical and clinical studies.

Herein we describe the synthesis of a series of tumor-targeted DON prodrugs that were designed to circulate intact and inert in plasma and be cleaved to DON preferentially in tumor cells. Our best prodrug **1** showed stability in plasma, liver and intestinal homogenates, yet was readily cleaved to DON in tumor cells. When directly compared to DON, prodrug **1** exhibited a 27-fold enhanced tumor cell-to-plasma ratio.



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2-ACYLAMINO AND 2-ALKYLAMINOBENZOTHIAZOLES AS NOVEL AGENTS TO SUPPRESS THE GENERATION OF PROSTAGLANDIN E2

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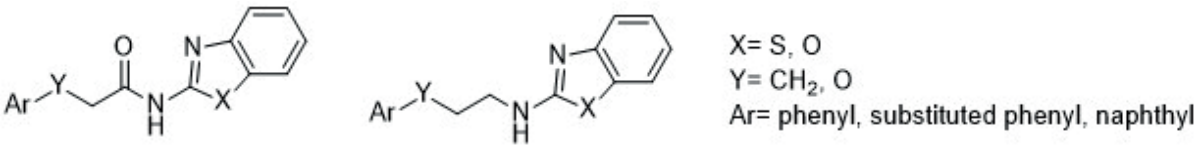
Prostaglandin E_2 (PGE_2) is one of the most important lipid mediators playing a pivotal role in a wide range of processes associated with inflammation, pain and cancer [1]. PGE_2 is overexpressed in various tumors, where chronic inflammation has been linked to the growth of cancerous tissues, and it has been identified as the major prostaglandin associated with the progression of various tumor malignancies including those of colon, lung and breast. As a consequence, there is an increasing interest in the discovery of novel agents targeting the PGE_2 signaling pathway [2]. The benzothiazole ring constitute a versatile scaffold for experimental drug design, thus attracted our interest to develop novel agents able to suppress PGE_2 generation.

A variety of 2-acylamino benzothiazole derivatives as well as 2-alkylamino benzothiazoles were synthesized and evaluated for their ability to inhibit in cells the production of PGE_2. 2-Acylamino benzothiazoles were synthesized by coupling of 2-aminobenzothiazole with various carboxylic acids carrying an aromatic ring, whereas 2-alkylamino benzothiazoles by reductive amination of aldehydes with 2-aminobenzothiazole. The effect of the compounds synthesized was tested in rat renal mesangial cells, which were stimulated by interleukin-1 plus forskolin to trigger a huge increase of PGE_2 synthesis. Potent inhibitors of PGE_2 generation were identified and the potency of the effect depends on the distance of the aromatic system from the benzothiazole ring and the substitution of the aromatic system.



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DEVELOPMENT OF SMALL MOLECULE ALLOSTERIC BETA 2 ADRENOCEPTOR MODULATORS

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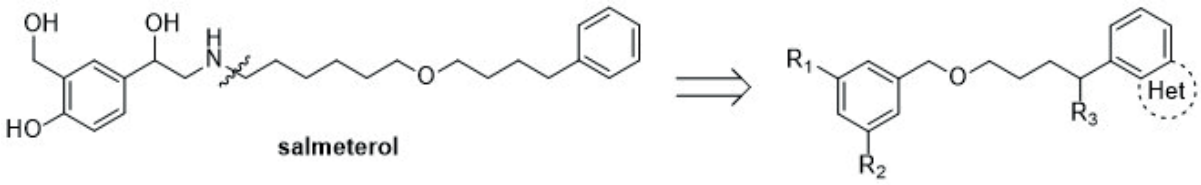
Bronchoconstriction is a major symptom in diseases like COPD and bronchial asthma, which can be effectively treated with selective β_2AR agonists, like salbutamol or the long-acting agent salmeterol.[1,2] The β_2AR belongs to the class of G protein-coupled receptors. A high resolution crystal structure of the β_2AR bound to the partial agonist salmeterol reveals that the saligenin ethanolamine moiety binds to the orthosteric binding pocket, whereas the hydrophobic aryloxyalkyl appendage interacts with an allosteric site of the receptor, which is topographically distinct from the orthosteric site. Interestingly, an identical allosteric pocket has not been identified in the β_1AR.[3] Thus, addressing this site can lead to receptor subtype selectivity, which displays a major advantage of allosteric modulators, as allosteric binding pockets are typically less conserved in their sequence than orthosteric sites.[4]

We developed small molecule allosteric modulators targeting the exosite of salmeterol. Taking advantage of the β_2AR-salmeterol crystal structure [3], novel ligands were designed in an iterative docking approach by formally removing the orthosteric moiety of the salmeterol template and modifying the aryloxyalkyl appendage. Hence, we designed compounds bearing a variety of heterocycles connected to differently substituted benzyl ethers by an alkyl linker. Various derivatives were synthesized and their allosteric effects were investigated in functional assays at the β_2AR, and its congener β_1AR.



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LIGANDS OF G-QUADRUPLEXES ON HETEROARENE-FUSED ANTHRAQUINONES

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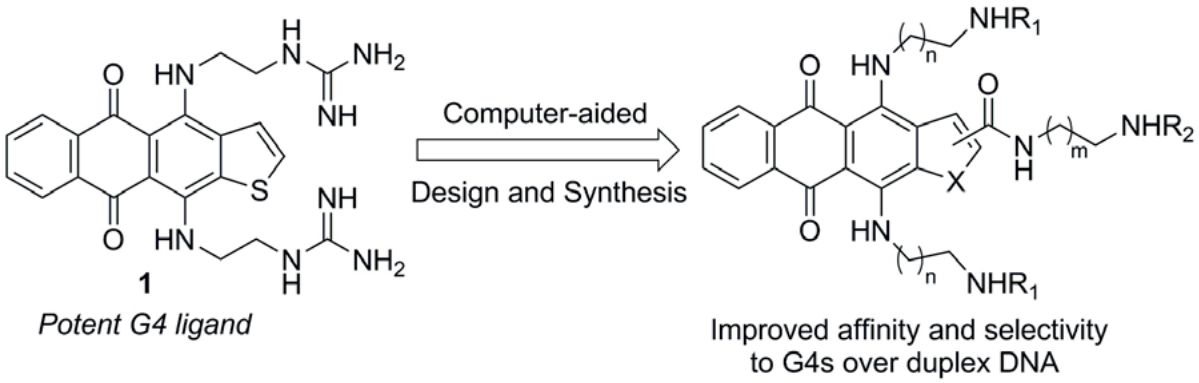
Nucleic acid G-quadruplexes (G4) attract a high attention for the development of new chemotherapeutic drugs. Originally, G4s were observed in nucleotides of telomere region of chromosomes, promoters of the oncogenes c-Myc, KIT, BCL-2, K-Ras, H-Ras, etc. Recently the folding of G4s was proved for viral RNA of Zika Virus, Ebola Virus, HIV-1, papillomaviruses and many others. Moreover, new putative G4-forming sequences that produce stable G4 structures were identified in genome of Trypanosoma brucei and Plasmodium falciparum. Thus, the design and study of new G4 ligands is a promising direction of medicinal chemistry.

Among the scope of all scaffolds the anthraquinone moiety represents one of the first and extremely productive chemical structure for a design of new G4-aimed ligands. Previously, an ability of anthra[2,3-*b*]thiophene-5,10-dione derivatives to interfere with G4s was identified. The hit-compound **1** demonstrates a strong affinity to DNA and RNA G-quadruplexes [1,2]. To optimize the structure of ligands we synthesized a series of heteroarene-fused anthraquinone (heteroareneanthraquinone) derivatives bearing a different number of side chains at 2,3,4,11-positions. The heterocyclic core, structure of terminal groups and length of spacer fragment were varied. Evaluation of binding with different G4-forming sequences (telomeric G4, Myc, Kit, TERT, K-ras, etc.) was carried out by the FID, FRET-melting assay and CD. In order to clarify the mechanism of complexation and improve affinity of the ligands docking and molecular dynamics procedures were used. Our efforts in the structure optimization gave new derivatives with stronger affinity for telomeric G4 (4 to 15 times) and significantly improved specificity to the quadruplexes over duplex DNA (up to 75 times) [3]. Moreover, several heteroareneanthraquinones demonstrated a preferential binding to some of G4s (e.g., TERT) compared to other nucleotide sequences. Screening of antiproliferative potency against different tumor cell lines revealed that new ligands inhibit growth at the low micromolar concentrations that indicates prospective for targeted anticancer therapy.



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MACROLIDE INSPIRED MACROCYCLES: DESIGN AND BIOLOGICAL EVALUATION

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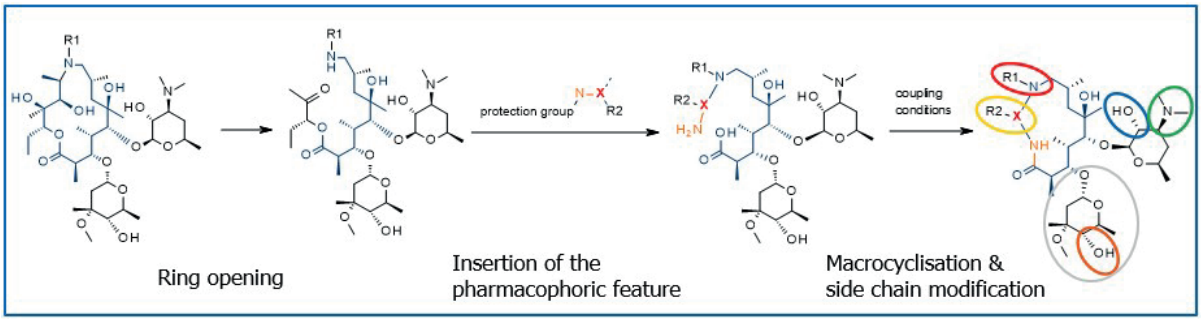
Macrocyclic molecules have unique properties that have proven effective in targeting protein-protein interactions (PPIs) [1]. Although they do not fit into the Lipinski "Rule of 5", they do have druggable PhysChem properties [2].

Novel macrolide inspired macrocyclic library is prepared using FideltaMacroTM technology. It was built using our long-term experience and in-house knowledge on the chemistry and pharmacology of this class [3-5].



Macrocycles are designed to diversify and enrich chemical space with different ring sizes, a variety of 3D shapes and potential pharmacophoric features with the aim to maintain the attractive PK and ADME profile. PhysChem properties have been measured and modulated using high-throughput chromatographic determination of lipophilicity and permeability parameters. Target based approach as well as phenotypic screening in anti-inflammatory area has been performed and several promising chemical scaffolds have been identified.

We will present recent results on the first generation of our macrolide inspired macrocyclic library including *in vitro* screening, pharmacokinetic data as well as *in vivo*proof of concept.

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PHOTOCATALYTIC SYNTHESIS OF gamma-LACTONES FROM ALKENES

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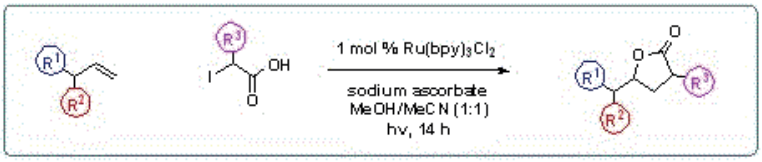
gamma-Lactones are very important moieties found in natural products, products of biological importance, perfumes and food additives. In literature, many synthetic approaches for the synthesis of lactones have been devised, utilizing as starting materials a variety of organic compounds. However, olefins are among the most popular synthetic blocks. Our laboratory has a long interest in Photocataysis and has recently reported a protocol for the intermolecular synthesis of *gamma*-lactones from olefins and iodo-acetic acid via photoredox catalysis, taking advantage of the ATRA reaction. Utilizing $Ru(bpy)_3Cl_2$ as the photocatalyst, a cheap and reproducible synthetic pathway for *gamma*-lactones has been introduced. Mechanistic studies revealed the successful monitoring of photocatalytic reactions and radical intermediates via High Resolution Mass Spectrometry (HRMS).[1]



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COMPUTER-AIDED DRUG DESIGN OF SMALL-MOLECULE NEUROTROPHIN MIMETICS

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Neurotrophins are growth factors that are expressed in the central and peripheral nervous systems. Among their roles are the control of dendritic growth and synapse formation and, ultimately, cell survival and apoptosis. Neurotrophins bind selectively to the three tropomyosin receptor kinase (Trk) receptors, TrkA, TrkB, TrkC, and collectively to the p75 receptor. Usually, binding to Trk receptors leads to cell protection and survival, while binding to the p75 receptor leads to apoptosis.[1,2] In neurodegenerative diseases, apoptotic cells show a decline in Trk receptor expression, so there has been an effort to treat neurodegenerative diseases with neurotrophins as therapeutic agents. However, this effort is hindered by the poor pharmacokinetic profile of neurotrophins, and their ability to induce immune reactions. For this reason, the use of small molecules as neurotrophin mimetics has been followed.[2] One class of neurotrophin mimetics is neurosteroids, and especially dehydroepiandrosterone (DHEA), which has been shown to protect cells against apoptosis via interaction with NGF receptors.[3,4] DHEA, however, can be metabolized to androgens and estrogens, so there is the need to modify the molecule. BNN-27 is a lead compound that possesses a modification at the C17 position of DHEA, thus abolishing unwanted metabolism.[5] BNN-27 has been shown to protect cells against apoptosis, acting selectively through the TrkA and p75 receptors.[6,7] The aim of our studies is to understand the molecular mechanism of action of BNN-27, from binding to causing an effect, as well as optimizing it for increased affinity and selectivity. For this purpose, docking studies have been carried out in order to assess probable binding sites for BNN-27. Moreover, derivatives and molecular fragments have been docked to deduce a basic Structure-Activity Relation and guide the design of analogues of BNN-27.

Acknowledgement

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A NEW THERAPEUTIC APPROACH FOR ALZHEIMER'S DISEASE: NOVEL P2X7 RECEPTOR ANTAGONISTS

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Etiology of the Alzheimer's disease (AD) is not fully understood. It has been revealed that the inflammation in the early stages is its major component. Therefore, the identification of anti-neuroinflammatory drugs could lead to novel treatments for AD. (1)

The P2X7 receptors (P2X7R) are implicated in the regulation of inflammatory response playing a crucial role in the neurogeneration process. These receptors belong to the family of ionotropic receptor being present on neurons, microglia cells and macrophages. The activation of the P2X7R by ATP in high concentration leads to increased cytokine IL-1β, making this receptor an attractive therapeutic target to reduce neuroinflammation. (2) In spite of a variety of potent antagonist P2X7R have become available and several of them have entered clinical trials, so far, none has been tested against Alzheimer's disease. (3)

Bearing in mind the aforementioned problem, the knowledge that adamantane moiety is a common structural feature in several P2X7 antagonists and the expertise of our group in polycyclic hydrocarbons, we decided to design, synthesize and pharmacologically evaluate a series of analogues of known Abbott's adamantane P2X7 antagonist **1**.(4) Replacement of the adamantane subunit of **1** led to our new hit **2**, endowed with higher potency (IC_{50} = 0.3 nM) (Figure 1).

Compound 1 IC_{50} = 10 nM

Compound 2 IC_{50} = 0.3 nM

Scaffold I

Considering the presence of the hydrazine moiety, that may rise toxicity issues (5), we also explored alternative safer linkers. Herein, we will present new derivatives of the **scaffold I** (Figure 1) studying the effects of the length and nature of the linker. Furthermore, additional *in vitro* assays were performed in order to discover a suitable candidate for *in vivo* studies to treat AD.

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HYBRID VIRUS-LIKE PARTICLE HEPARIN ANTAGONISTS

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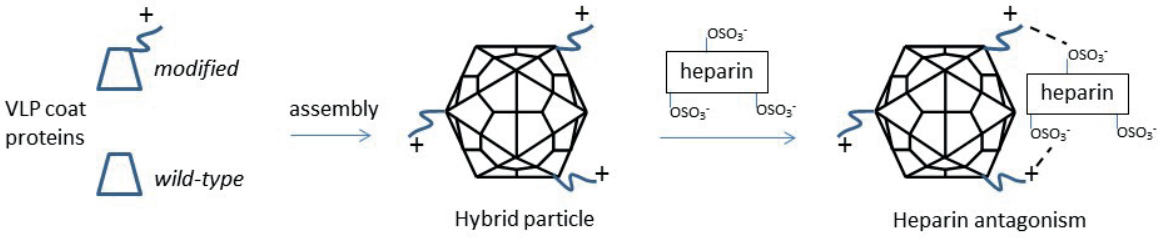
Virus-like particles (VLPs) have many applications in medicine and biology. The reliable, symmetric self-assembly mechanism of VLPs and the ability to take advantage of surface functionalities, through either chemical modification or mutation, provides for a versatile scaffold. Exploiting these desirable attributes, we have designed hybrid VLPs for use as potent heparin antagonists. A two-plasmid system was utilized to generate VLPs that contain both the wild-type coat protein and a second coat protein with either a C- or N-terminal cationic peptide extension (4-28 amino acids). Incorporation of the modified coat proteins varied from 8% to 31%. Activated partial thromboplastin time (APTT) assays revealed a range of heparin antagonist activity for the various particles. However, when examined based on the quantity of peptide delivered due to the varied incorporation rates it appeared that the VLPs largely followed a similar trend, with the quantity of peptide delivered more closely correlating with heparin antagonist activity. The particle with the highest incorporation rate and best anti-heparin activity displayed the C-terminal peptide ARK_2A_2KA; this sequence corresponds to the Cardin-Weintraub consensus sequence for binding to glycosaminoglycans. Analysis of this particle using heparin affinity chromatography revealed that particles eluting at higher salt concentration had a greater proportion of peptide incorporation. Preliminary dual polarization interferometry experiments also support a strong interaction between this particle and heparin. These results encourage further exploration of VLPs as heparin antagonists, and more generally validate the development of VLPs for targeted medical use.



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MODIFYING THE 4-ANILINOQUINAZOLINE SCAFFOLD FOR BRAIN PENETRATION: DEVELOPMENT OF A POTENT EGFR TYROSINE KINASE INHIBITOR FOR THE TREATMENT OF GLIOBLASTOMA

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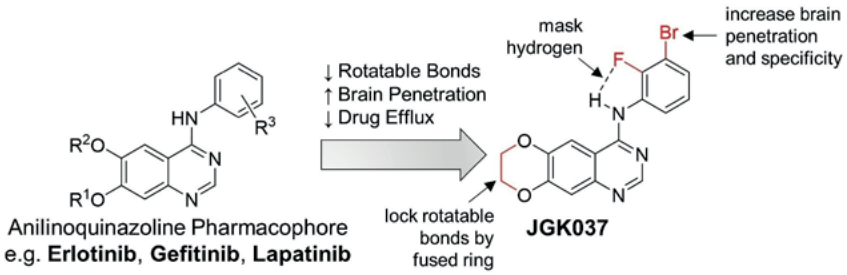
Glioblastoma (GBM) is the most common malignant brain tumor in adults and the most lethal. Genetic analysis revealed that EGFR is altered in nearly 60% of GBM patients, but despite the clinical success of EGFR tyrosine kinase inhibitors (TKIs) for the treatment of lung or breast cancers, these drugs have failed for GBM patients. This failure is largely attributed to the fact that these drugs do not readily cross the blood-brain-barrier (BBB), thereby not achieving pharmacological levels for a tumor response in the brain. Herein, we report on the identification of our lead compound **JGK037**, which is a brain-penetrant EGFR TKI. **JGK037** emerged from a physicochemical property-guided structure-activity relationship analysis to identify optimal properties for CNS activity. Our lead compound, **JGK037**, was developed based on the type I 4-anilinoquinazoline scaffold by rational modifications to improve brain penetrance and potency, namely ring fusion of the 6,7-dialkoxy groups to reduce the number of rotatable bonds and the polar surface area, and by introduction of an *ortho*-fluorine and a *meta*-bromine on the aniline ring. **JGK037** displayed high activity against EGFR mutant, GBM patient-derived cell cultures (HK301 GI_{50} ~300 nM), significant BBB penetration (2:1 brain-to-plasma), and superior efficacy in orthotopic GBM xenograft models relative to the conventional EGFR TKIs erlotinib and lapatinib.



Compound	HK301 GI_{50} (nM)	GBM39 GI_{50} (nM)	Brain Penetration (%)
Erlotinib	700	2788	8.5
Gefitinib	983	2793	1–2
Lapatinib	1290	2101	1.9
JGK037	**329**	**1116**	**211.8**

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HIGH-THROUGHPUT PHENOTYPIC SCREENING IN SHIGELLA FLEXNERI FOR THE IDENTIFICATION OF POTENTIAL NARROW-SPECTRUM ANTIBIOTICS FOR THE TREATMENT OF BACTERIAL ENTERIC INFECTIONS

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Diseases of the Developing World (DDW), Tres Cantos Medicines Development Campus (TCMDC), GlaxoSmithKline, Severo Ochoa 2, 28760 Tres Cantos, Spain

Enteric and diarrheal diseases are one of the leading causes of infant mortality in developing countries. Shigellosis is a gastrointestinal infection caused by one of the four species of *Shigella* bacteria. It is estimated that annually, it causes the death of 200,000 children under the age of five. Antibiotics such as tetracycline, ciprofloxacin, co-trimoxazole and nalidixic acid were previously highly effective. But currently, *Shigella* spp. have developed resistance against fluoroquinolones, cephalosporins and azithromycin. So, the emergence of antibiotic resistance demands the development of new and better antimicrobil drugs. Using *Shigella* as efficacy driver our objective is to develop drugs to treat moderate and severe diarrhoeal cases with bacterial etiology.

Herein, we present the results obtained from the high through-put phenotypic screening of the GSK compound collection (2M compounds). We have identified over 50 different chemical entities that were active in the assay. One of these chemotypes was found of great interest, as it came from an antibacterial program and it was known to target LpxC, a zinc dependent UDP-3-O-((R)-3-Hydroxymyristoyl)-N-acetylglucosamine deacetylase. LpxC is an essential enzyme in the lipid A biosynthetic pathway in gram-negative bacteria.

LpxC inhibitors open the door to guide drug discovery efforts towards obtaining new narrow-spectrum antibiotics that can treat bacterial enteric infections minimising gut microbiome alteration.

DEVELOPMENT OF NOVEL HDAC-RTK INHIBITORS FOR CANCER TREATMENT

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In the past few years, the development of mechanism-based targeted antitumor drugs has made significant progress. However, disease relapse and metastasis remain the main obstacle to cancer therapy. In addition, acquired drug resistance, due to the presence in the tumor mass of cancer stem cells, always limits the use of a single agent. The scientific community in the last period has shown a growing interest in the development of multitarget "Chimeric Drugs" formed by different pharmacophoric functions belonging to various drugs and the most important chimeric drug actually in clinical trial is CUDC-101. The pharmacophoric portions used belong to the therapeutic class of receptor tyrosine kinase inhibitors (RTKIs) and histone deacetylase inhibitors (HDACIs), because these two therapies had shown a synergistic effect when combined together. The TKI reference structures in this project derived from some ATP-mimetic kinase inhibitors recently discovered in our laboratory that showed high affinity toward class III RTKs (4-anilinopyrimidines) and class XIV RTKs (4-anilinopyridines)[1][2]. For HDAC inhibition, Panobinostat has been chosen as reference compound [3]; this drug is a pan-HDAC inhibitor approved as epigenetic regulator for the treatment of various cancers (*Figure 1*).

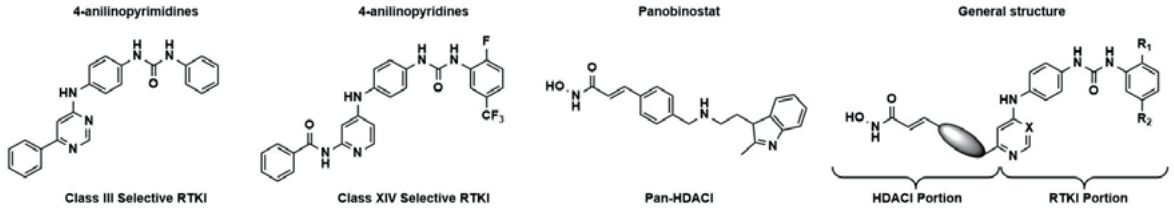

Fig. 1: References compounds and general structure of the synthetized compounds.

This new drug design approach relies on the merging process of different pharmacophoric functions belonging to various drugs, merged together on the solvent exposed portion. This leaves the original pharmacodynamic properties of the two starting molecules unchanged. By this way a small library of bifunctional molecule was then designed and synthesized (*Figure 1*) to maximize their effects on these two targets and optimize their pharmacokinetics properties. All the synthesized compounds are currently under biological evaluation in order to verify their selectivity profile against a kinase panel and their ability to function as epigenetic regulators of gene transcription

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PROBING GPCR'S: ADDING CHEMICAL BIOLOGY TOOLS TO THE MEDICINAL CHEMISTRY TOOLBOX

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G protein-coupled receptors (GPCRs) have been among the most popular drug targets for decades, mostly due to their involvement in many of the essential signaling pathways in the human body.[1] As a result, much is known about the structure and function of GPCRs and their respective ligands. In a recent paper, DPCPX, reported as selective antagonist for the adenosine A_1 receptor (A_1AR), was shown to increase proteasome activity.[2] This is an interesting finding as repetition of the experiment with A_1AR antagonists with a different scaffold did not show increased proteasome activity, suggesting that the action of DPCPX is unrelated to its interaction with the A_1AR. This finding on a prototypical GPCR ligand suggests that many known ligands might have unknown off-targets, prompting the need for more tools to accurately assess ligand selectivity, outside the commonly tested "close neighbor"-proteins. An affinity based probe (AfBP) might serve as such a tool. AfBPs consist of an electrophilic reactive group ('warhead'), that is able to covalently bind nucleophilic amino acid residues, and a label ('reporter tag'), that allows for the detection of protein molecules after the probe has bound (figure 1).

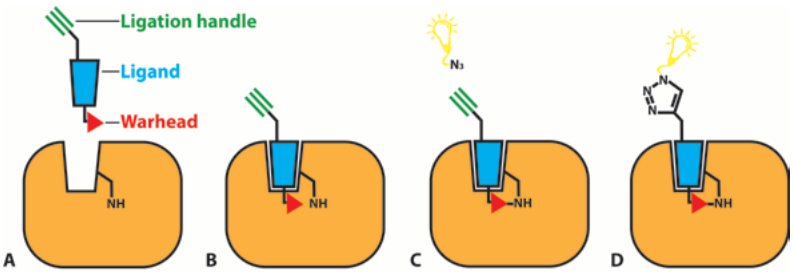

Figure 1: Schematic representation of the process of affinity-based protein profiling starting with an unbound affinity-based probe and unoccupied binding site (A). After affinity-driven association of the ligand to the receptor (B), the warhead will covalently bind to a nucleophilic amino acid residue in the binding site (C). Lastly, the irreversibly bound ligand will be coupled to a reporter group via a click reaction (D).

The concept of affinity based protein profiling is drawn from the field of chemical biology, where activity based probes have been used for decades. Combined with click chemistry, these probes can be used to profile many proteins (mainly enzymes) and enhance our understanding of target localization and engagement.[3] For GPCR's, this technique is currently not widely used as only few probes have been developed and applied, with varying levels of success.

Working on the prototypical family of the adenosine receptors, GPCR's that are widespread and ubiquitously expressed throughout the body, we set out to develop a set of tools to probe these receptors and set the stage for applications on other GPCRs. In this endeavor, we have previously developed an AfBP for the adenosine A_{2A} receptor ($A_{2A}AR$)[4] and are currently working to follow up our research on the development of covalent ligands for the A_1AR. Here we present the synthesis and application of the first affinity base probe for the $A_{2A}AR$ and our progress towards a new set of potential probes for the A_1AR is discussed. Taken together these results are great steps towards adding chemical biology tools to the medicinal chemistry toolbox.

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DEVELOPMENT OF NOVEL NS2B-NS3 PROTEASE INHIBITORS OF DENGUE AND ZIKA VIRUS

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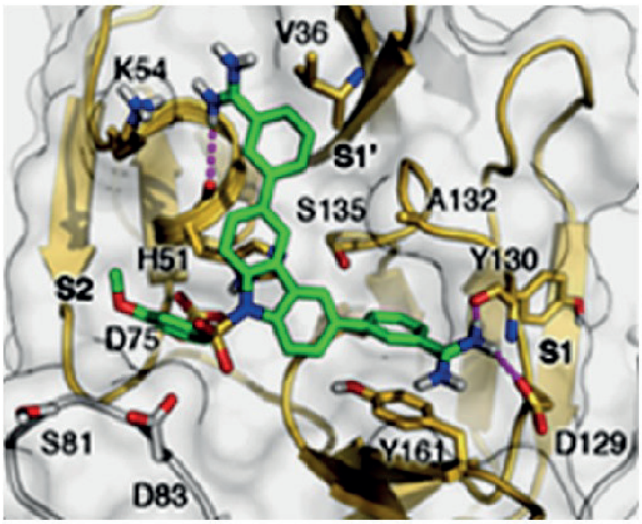
The Flaviviridae family includes viruses such as dengue, zika, yellow fever and West Nile for which there are currently no treatments available and constitute an unmet medical need for more than 2 billion people living in tropical and subtropical areas. In this case, small-molecule antivirals appear as the most promising approach especially since vaccine development is confounded by cross-reacting antibodies. Prompted by the conserved nature of the viral NS2B/NS3 protease across all flaviviruses we pursued development of small molecule pan-flaviral inhibitors. Starting with an earlier urea-bis-amidine hit we performed a scaffold hopping exercise which led to a carbazole bis-amidine with DENV2pro IC_{50} 1.16 uM and ZIKVpro IC_{50} 0.52 uM. Targeted SAR yielded several low toxicity carbazole bis-amidines with significant cellular activity against both DENV and ZIKV. In order to improve the solubility and permeability in our series we identified appropriate pro-drugs through bioisosteric replacement of the amidine groups with amidoximes. Our best current lead exhibits potent dual inhibition, increased safety (SI>140 μM) and significant cell-efficacy against both DENV2 and ZIKV (EC_{50} 0.35 and 7.78uM respectively). This is one of the best profiles among all published NS2B/NS3 protease inhibitors in the literature and constitutes a significant advancement towards a pan-flaviviral protease inhibitor.



PRENYLATED POLYPHENOLS WITH ANTIBACTERIAL ACTIVITY AND THEIR ABILITY TO COMBAT STAPHYLOCOCCUS AUREUS RESISTANCE TO COMMERCIAL ANTIBIOTICS BY GENERATING REACTIVE OXYGEN SPECIES (ROS)

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For several decades, antimicrobial resistance (AMR) has been a growing threat to the effective treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi. AMR results in reduced efficacy of antibacterial drugs, making the treatment of patients difficult, costly, or even impossible. Use of antimicrobial drugs has become widespread over several decades, and these drugs have been extensively misused in both humans and food-producing animals in ways that favor the selection and spread of Multidrug-resistant (MDR) bacteria. [1]

One of the most common and frequent antibiotic-resistant bacteria is methicillin-resistant Staphylococcus aureus (MRSA). According to reports, MRSA causes more deaths than the human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), emphysema, homicide and Parkinson's disease. [2]

In recent years, it has been proposed that reactive oxygen species (ROS) have a high correlation with the mechanisms of antibiotics and bacterial death. [3] The increase of the levels of intracellular ROS through the endogenous inhibition of antioxidants, the modulation of the functions of the proteins responsible for the maintenance of redox homeostasis and the use of small molecules as ROS generating sources have proved very successful in the therapeutic field. The combination strategy is another route to regulate drug resistance. Combinations of ROS inducers and commercial drugs have shown great promise in selectively killing bacteria with greatly improved inhibitory potential.

Therefore, small molecules that modulate antioxidant levels and/or improve intracellular ROS could alter the bacterial oxidative environment and induce bacterial death, and therefore could serve as new therapies.

Polyphenols have antioxidant activity (radical uptake and metal chelating activity) or pro-oxidant activity depending on environmental conditions, interaction, structural changes, and exposure to microorganisms. [4]

Our research group has found that prenylated polyphenols (acetophenones, phenylethyl ketones, flavonoids, isoflavonoids) were more active than the same non-prenylated compounds in MRSA strains and also were found to act synergistically with commercial antibiotics such as methicillin, vancomycin, and ciprofloxacin, reducing the MIC of MRSA in more than 1000 times. Important structural features that were found were the presence of catecholic hydroxyl groups, lipophilic groups such as the prenyl group and the benzopyran-4-one skeleton. It was also found that from a series of prenylated polyphenols tested, those that resulted in the greatest bacterial growth inhibition activity was also generated the highest levels of intracellular ROS.

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STRUCTURAL EXPLORATION OF CINNAMATE-BASED PHOSPHONIC ACIDS AS INHIBITORS OF BACTERIAL UREASE

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The conjugated system of cinnamic acid, α-substituted with a phosphonoalkyl residue, was previously validated as a scaffold which provided one of most potent organophosphorus inhibitor of bacterial urease. Following the idea of employment of reactivity of Morita-Baylis-Hillman adducts to introduce the terminal phosphonic side chain functionality to the α,β-unsaturated system we currently report the synthesis and activity of extended compounds. Cinnamates modified with 3-phosphonopropyl and 4-phosphonobutyl side chains were obtained in a convenient two-step procedure which involved Pd-mediated transformations of the Morita-Baylis-Hillman bromides as the key substrates. A submicromolar ligand of *Sporosarcina pasteurii* urease (K_i = 0.509 μM) was identified among the active molecules. Basing on the structure-activity relationship and the mechanisms of inhibition we suggest a non-typical mixed mode of action for the slow binding compounds.

We presume that the molecular distance between phosphonic group and the backbone double bond allows a double activity: complexation of the acidic group with nickel ions and the Michael addition with thiolate of the cysteine forming the active site lid.

Acknowledgement

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL LIPOYL/POLYPHENOLIC HYBRIDS

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Lipoic Acid (LA) is a natural disulfide compound present in almost all foods from animal and vegetable sources and plays an important role in pathological conditions characterized by oxidative stress such as: (i) scavenger of ROS, (ii) capacity to increase the level of reduced glutathioneand other antioxidant enzymes, (iii) downregulation of the inflammatory processes, (iv) scavenging of lipid peroxidation products, (v) redox active transition metal chelation, (vi) increase of ACh production by activation of choline acetyltransferase. On the basis of such activities, LA can exert beneficial effects in AD, possibly stabilizing cognitive functions. Several lipoyl-phenolic acid hybrids were synthesized and tested for their neuroprotective ativity. Caffeic acid, ferulic acid and 3,4-dihydroxyphenylacetic acid were tethered through a linker to lipoic acid.

Biological evaluation towards neurodegenerative diseases and stability control are underway.

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SYNTHESIS OF AI-2 DERIVED PRODRUGS AND CHEMICAL PROBES

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Autoinducer-2 (AI-2),[1,2] is a signalling molecule for bacterial inter-species communication. Understanding the molecular mechanisms that bacteria use to communicate and therefore regulate their group behaviours can lead to the development of new therapies to control bacterial infections. Based on previous results, we hypothesise that AI-2 plays an important role in controlling colonisation and homeostasis of the gut microbiota contributing to the protective properties of this poly-species environment against pathogens.[1] Here we present the synthetic strategy to obtain new beta glycoside analogues of AI-2 (Fig. 1) that will function as prodrugs to deliver intact AI-2 to the gut, taking advantage of beta-glycosidases produced there. The anomeric selectivity of the glycosylation reaction between suitable AI-2 precursors and several different thioglycosides has been studied to obtain preferentially the beta anomer.

Another aim is to develop chemical probes based on the AI-2 structure using different synthetic strategies (Fig. 1). These probes will allow the identification of new AI-2 receptors. Despite being widely expressed, at the moment only two classes of protein receptors for AI-2 have been identified, LuxP and LsrB.[1,3] We describe the synthesis of new AI-2 derived molecules that will either allow the modulation of gut microbiota composition or increase the knowledge on AI-2 mediated bacterial quorum sensing. Both approaches will be relevant for the development of new and effective strategies to manipulate bacterial behaviours.

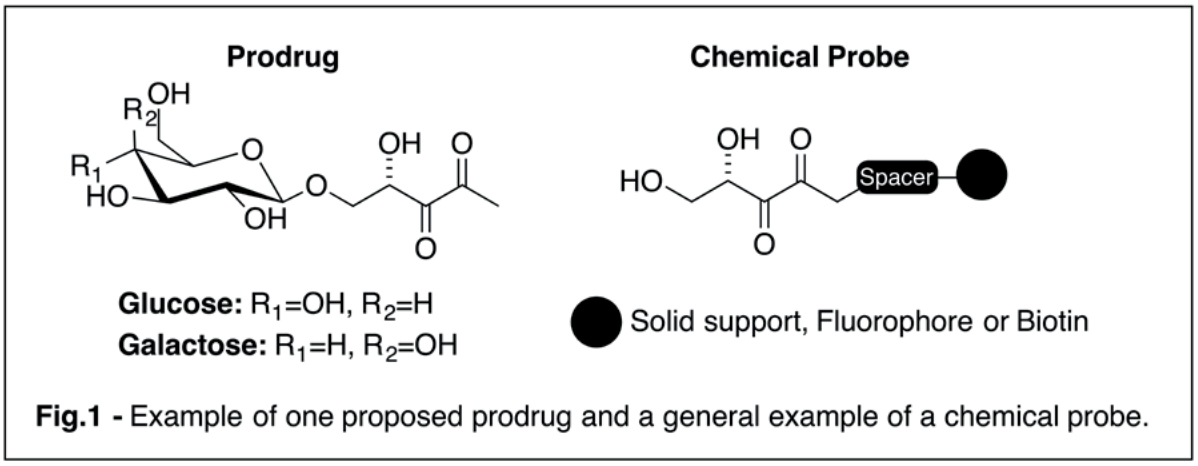

Fig.1 - Example of one proposed prodrug and a general example of a chemical probe.

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PYRROLO[2,3-b]PYRIDINES AS POTENT INHIBITORS OF ADAPTOR ASSOCIATED KINASE 1 (AAK1) WITH ANTIVIRAL ACTIVITY

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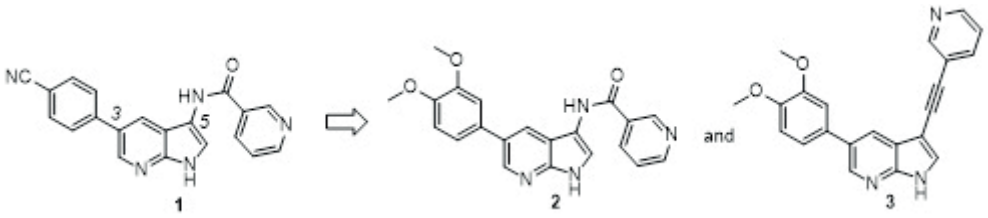
Adaptor associated kinase 1 (AAK1) is a cellular serine/threonine kinase that regulates the clathrin mediated endocytosis of multiple unrelated RNA viruses. Clathrin mediated endocytosis is an essential cell entry process in which a cell can take up metabolites, proteins and hormones, normally unable to be incorporated by normal diffusion over the cell membrane. Several viruses are known to hijack this pathway to enter their host cells for infection. The specific overexpression of AAK1 in virus infected cells makes it a potential antiviral target protein[1][2]. In order to validate the concept that AAK1 inhibition offers the potential of developing broad-spectrum antiviral agents, we embarked on an medicinal chemistry optimisation campaign aiming at the discovery of AAK1 inhibitors with antiviral activity.

Starting from a known and reasonably potent AAK1 inhibitor (compound **1**, Kd = 120 nM), a systematic structural variation at positions 3 and 5 of the pyrrolo[2,3-*b*]pyridine scaffold was carried out. It led to the discovery of two novel 7-azaindole analogues (compounds **2** and **3**) that both display very potent AAK1 inhibition (IC_{50} of 4 nM for both analogues). These AAK1 inhibitors display antiviral activity against the dengue virus in the low micromolar range. Moreover, they are endowed with potent activity, when their antiviral efficacy was investigated in dengue virus infected human primary monocyte-derived dendritic cells, that are physiologically a more relevant model. In addition, the optimized AAK1 inhibitors show remarkable antiviral activity against the Ebola virus, confirming the hypothesis that broad-spectrum antiviral agents can be discovered by targeting AAK1.



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A NEW CLASS OF POTENT AND SELECTIVE HDAC6 INHIBITORS: SAR ANALYSIS AND DOCKING RESULTS

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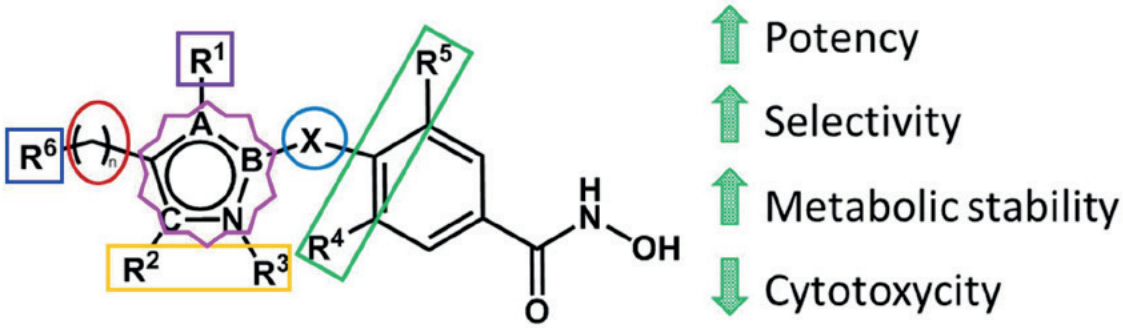
The human histone deacetylase 6 (hHDAC6) is the only isoform, among the Zn-dependent deacetylase family members, that features two catalytic domains and a ubiquitin binding Zinc-finger domain. It is usually localized in the cytoplasm and it acts mainly on non-histone substrates, like tubulin, Hsp90, cortactin and the transcription factor foxp3. By regulating the acetylation state of these and other important proteins, it orchestrates many different physiologic functions, like microtubules dynamics and immune system homeostasis. HDAC6 is an interesting therapeutic target, as it has a pathogenic role in many different diseases. Furthermore, HDAC6 KO mice are viable, implying that the inhibition of the enzyme may be well tolerated. Accordingly, a number of HDAC6 selective inhibitors are under investigation for the treatment of auto-immune diseases, such as lupus,[1] myasthenia gravis, rheumatoid arthritis[2] and GVHD,[3] oncological disorders, such as melanoma[4] and multiple myeloma,[5] and some CNS syndromes, like Huntington's and Alzheimer's diseases.[6] Moreover, their activity as immune checkpoint modulators is also under exploration.[7]

We have recently discovered a new class of potent and selective benzohydroxamate-based HDAC6 inhibitors with a pentaheterocyclic scaffold (see the figure below).[8]We present here the SAR analysis and docking results on this class of compounds, showing the importance of a methylene or sulfur bridge between the central pentaheterocycle and the benzohydroxamic moiety, the right metric between the cap-term and the central core and, especially, the influence of the benzohydroxamic ring fluorine substitution on the selectivity over the other HDAC isoforms.



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SYNTHESIS OF ENANTIOMERICALLY PURE STEREOISOMERS OF (5-ALKYLPYRROLIDIN-2-YL)BENZYL ALCOHOLS

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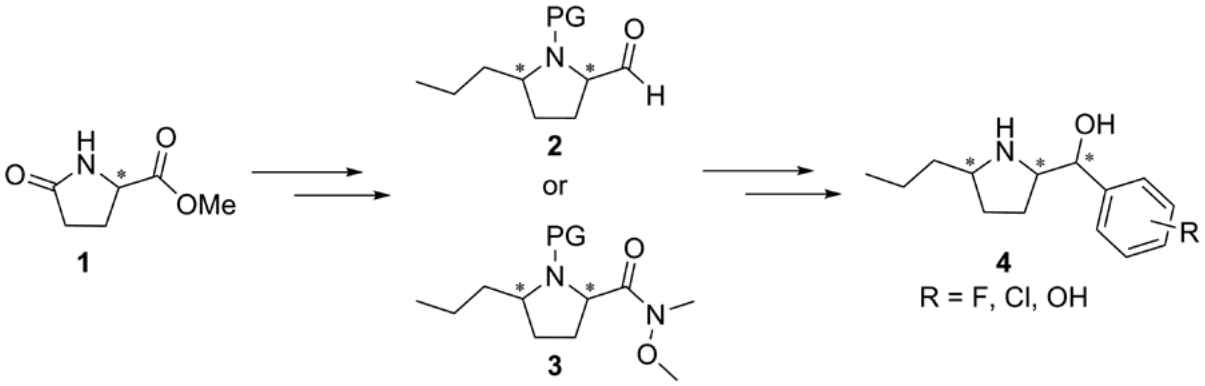
The β-amino alcohol motif is found in many biologically important compounds from natural and synthetic origin, as well as in ligands and auxiliaries for asymmetric synthesis.[1] Locking the conformation of the active fragment in bioactive molecules may increase the potency and selectivity towards target receptor. Therefore, our main focus was the synthesis of β-amino alcohols in which the motif is combined with a pyrrolidine cycle. With three possible stereocenters in target compounds **4**, the main goal of our work was to develop a method for the synthesis of all possible stereoisomers.



Our strategy towards target compounds started with (*R*)- or (*S*)-pyrroglutamate **1** which in 5 or 7 steps was transformed into aldehyde **2** or Weinreb amide **3** respectively. Diastereoselective introduction of the propyl group was crucial to ensure *cis*- or *trans*-configuration relative to the existing stereocenter.[2] In further transformations, amino alcohols were obtained as mixtures of *syn*- and *anti*-diasteromers, which were successfully separated and characterized, after deprotection giving target compounds **4**.[3] The two routes, i.e., starting from aldehyde **2** and Weinreb amide **3**, were studied and compared in terms of selectivity and efficiency.

This work is realized in frame of the project “Super Biased Ligands for Treatment of Type II Diabetes”, E! 10635 SUBERB, which is supported by Eurostars, a joint programme between 36 participating states and the European Union that supports international innovative projects.
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ORGANIC LOW MOLECULAR WEIGHT BIOACTIVE COMPOUNDS AS ANTAGONISTS OF ADENOSINE TRIPHOSPHATE

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Protein kinases are enzymes that play pivotal role in cell functions regulating many signal pathways by inducing ATP phosphorylation. Dysregulation of protein kinases and their receptors activity has been related to various diseases such as cancer. Inhibition of these pathological protein kinases through small molecular weight compounds that compete the ATP binding site in the kinase active core is found to contribute in the treatment of the disease symptoms. For this reason, there is great interest in the scientific community for the synthesis and development of new more potent protein kinase inhibitors, acting selectively in the pathological protein kinase. In other words, the selective inhibition of protein kinases has been established as one of the most promising targeted therapeutic strategie for treating diseases.

Imatinib (Gleevec) is the first selective inhibitor who antagonizes the ATP binding site in the pathological Bcr-Abl tyrosine kinase in the treatment against Chronic Myeloid Leukemia (CML). Nilotinib was designed as a second generation selective Bcr-Abl kinase inhibitor and exhibits greater inhibitory activity compared to Imatinib.

In addition Osimertinib, a new FDA-approved medicinal product, is an irreversible selective protein kinase inhibitor administered to patients afflicted with non-small cell lung cancer.

New compounds, Nilotinib analogues/derivatives, will be synthesized in the laboratory, as a result of molecular modeling in order to act more effectively on the protein kinases targets, aiming at their selective inhibition. These modifications on the original pharmaceutical compounds are targeted at the final phenyl ring, where amino acids that increase the hydrogen bonds and the aromatic ability are attached. Additionally, efforts will be made to develop an optimized synthesis of Osimertinib and analogues, with an expected stronger and more selective inhibitory effect.

ORGANOCATALYTIC OXIDATION OF SUBSTITUTED ANILINES TO AZOXYBENZENES AND NITRO COMPOUNDS: MECHANISTIC STUDIES EXCLUDING THE INVOLVEMENT OF A DIOXIRANE INTERMEDIATE

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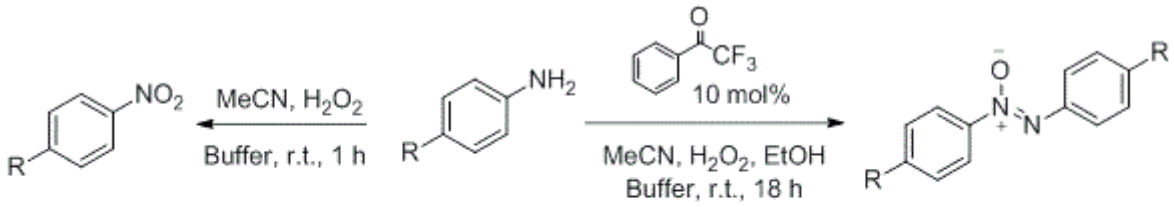
Nitro compounds have always been considered as ideal intermediates in Organic Synthesis, finding numerous industrial applications.[1] In the literature, the oxidation of anilines can be performed using dimethyldioxirane,[2] which converts primary amines and substituted anilines to nitro compounds in a facile, mild and high-yielding process. On the other hand, azoxy compounds can be successfully produced from the corresponding nitro compounds.[3] However, the oxidants needed are either expensive or produce large amounts of waste raising environmental issues. Herein, an organocatalytic and environmentally friendly approach for the selective oxidation of substituted anilines is presented.[4] Utilizing a 2,2,2-trifluoroacetophenone-mediated oxidation process, substituted anilines can be transformed into azoxybenzenes, while a simple and facile protocol utilizing MeCN and H_2O_2 leads to the corresponding nitro compounds, providing two friendly reactions that can be easily scaled up. Mechanistic studies utilizing HRMS were carried out constituting an indirect proof that the involvement of a dioxirane intermediate is excluded.



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GEMCITABINE-GnRH BIOCONJUGATES BEARING OXIME BOND LINKAGES: SYNTHESIS, IN VITRO STABILITY, DRUG RELEASE AND CYTOTOXIC EFFECT

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Cancer is the second leading cause of death worldwide and as a result a variety of strategies are currently being exploited to concur it. Current treatment processes involve a combination of treatments like surgical intervention, radiation and chemotherapeutic drugs. Notably, drugs used for this purpose are inevitably cytotoxic in order to eliminate cancer cells, but they lack selectivity and inevitably cause severe side effects on the patient's health. A rapidly emerging field of therapy involves Peptide-Drug Conjugates (PDCs), which are considered as an inextricable part of the oncologic armamentarium and are continuously explored as a viable approach to target malignant tumours[1, 2]. Gemcitabine is one of the most frequently used nucleoside analogues in chemotherapy for various types of solid tumors[3] but there are certain limitations in its usage mostly due to its collateral cytotoxicity, the drug resistance and its conversion to the inactive metabolite (dFdU). Towards this end, we rationally designed and synthesized three Peptide – Drug Conjugates bearing oxime bond, consisted of gemcitabine (drug), D-Lys^6-GnRH (tumour-homing peptide) and aminooxy acetic acid (acid-labile linker). This concept was based on the fact that D-Lys^6-GnRH selectively binds on GnRH-Receptor, overexpressed in various cancer cells[4], and gets internalized via endocytosis, dragging gemcitabine intracellularly and therefore surpassing the drug resistance limitation by introducing an alternative entrance path. To halt its unwanted deamination to dFdU, its free -NH_2 moiety was capped with the linker. Last, the utilized linker gets hydrolysed in the slightly acidic pH of the tumour microenvironment, enhancing the drug accumulation in malignancies. Finally, we evaluated the biological profile of the three conjugates regarding their *in vitro* cytotoxicity, stability in cell culture and human plasma, as well as their consequent drug release in prostate cancer cell lines.

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SYNTHESIS OF FUNCTIONAL BUILDING BLOCKS FOR PROTACs

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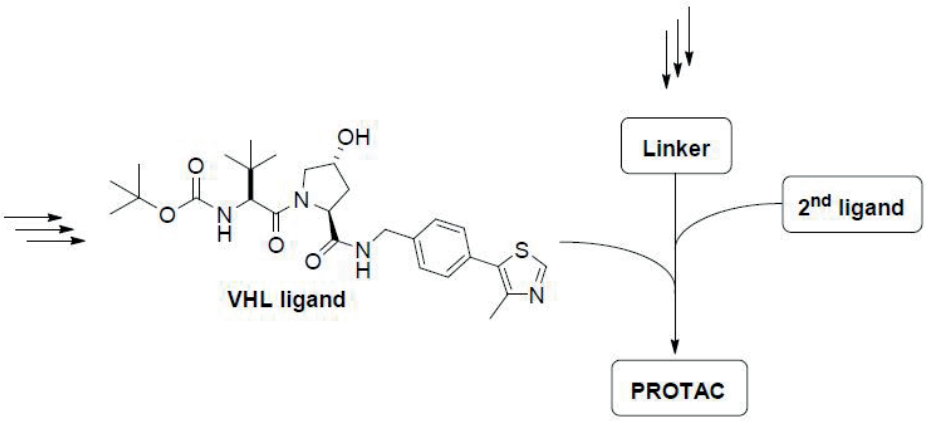
Proteolysis-targeting chimeras (PROTACs) are an emerging class of tool compounds and potential drugs. PROTACs are bifunctional small molecules that link an E3 ubiquitin ligase to a target protein of interest inducing its ubiquitination and subsequent proteasomal degradation. PROTACs consist of a target binding moiety, an E3 ubiquitin ligase recruiting ligand and a variable linker. Among the variety of human E3 ligases, the von-Hippel-Lindau (VHL) protein gained enormous importance in PROTAC development. It belongs to the family of cullin RING E3 ubiquitin ligases and targets e.g. hypoxia inducible factor 1α.[1]



Herein we report the synthesis of different building blocks which led to potent PROTACs and are applicable for our ongoing PROTAC projects. We show the synthesis of two diastereomeric VHL ligands needed to assemble VHL-addressing PROTACs and analogues which serve as negative controls. The preparation of α,ω-hetero-bifunctionalized linkers, their deprotection and utilization for the preparation of PROTACs is demonstrated.[2]

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COPPER-CATALYZED SYNTHESIS OF SUBSTITUTED 4-QUINOLONES USING WATER AS A BENIGN REACTION MEDIA: APPLICATION FOR THE CONSTRUCTION OF OXOLINIC ACID AND BQCA

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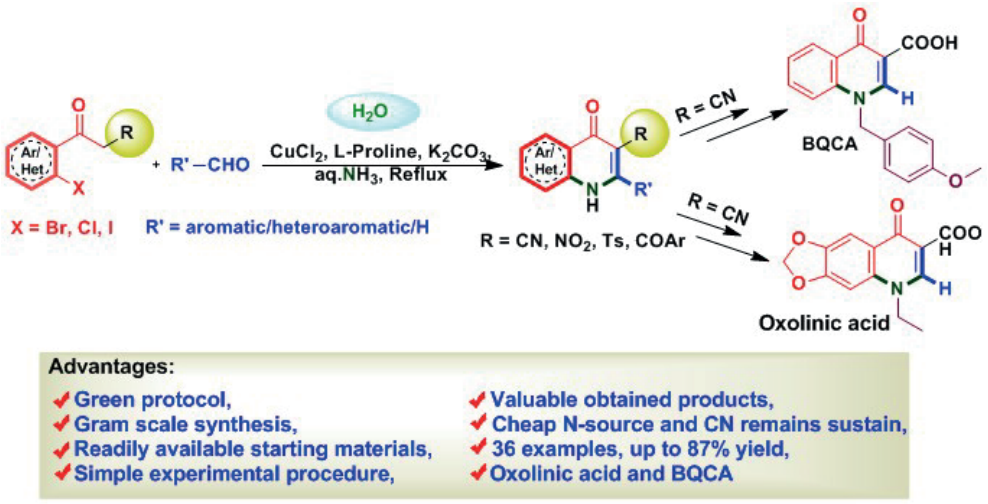
A copper-catalyzed three-component synthetic method has been developed for the synthesis of substituted 4-quinolone derivatives from substituted 3-(2-halophenyl)-3-oxopropane, aldehydes and aq. NH_3 using water as an environmentally benign reaction media. Moreover, the synthetic utility of the obtained products has been successfully applied for the synthesis of available oxolinic acid and BQCA drugs. The key features of this approach include commercially available starting materials, broad scope, and moderate to good reaction yields. Reaction with formaldehyde, and other functionalities such as -CN, -NO_2, -SO_2Ar, and -COAr were also successful. In addition, reaction with heterocyclic compounds such as 3-(3-bromothiophen-2-yl)-3-oxopropanenitrile proceeded smoothly to afford tetrahydrothieno[3,2-*b*]pyridine-6-carbonitrile analogues. The practicality of the designed protocol was confirmed by gram scale synthesis of two derivatives.



ISOCYANIDE WITH BORONIC ACID AND APPLICATION IN MCRs REACTION

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Multicomponent reactions (MCRs) are one-pot reactions employing more than two starting materials. Many basic MCRs are name reactions, such as Ugi reaction, Groebke-Blackburn-Bienaymé reaction (GBB reaction), Passerini reaction and so on. Among them, GBB reaction is used for the one-pot synthesis of therapeutically relevant fused imidazoles bridgehead nitrogen heterocyclic compounds from readily available aldehyde, isocyanide and amidine building blocks. So, the isocyanide is an important building blocks. On the other hand, the GBB reaction has seen diverse applications in combinatorial and medicinal chemistry and its products are of great use in drug discovery. Boronic acid as an interesting chemical group has been getting more and more attention from researchers. In our project, firstly, some formamides with boronic acid were synthesized to build the formamide building blocks. Then, these formamides were used to synthesize the isocyanides to get the important starting materials of GBB reaction. Finally, these isocyanides were reacted with different aldehydes and amide to get different GBB products. Thus, the isocyanide with boronic acid can be synthesized successfully and may increase the diversity of isocyanide that can be used in MCR reactions.

CAPSULE CHEMISTRY AT THE TOUCH OF A BUTTON - A NEW TOOL FOR MEDICINAL CHEMISTRY

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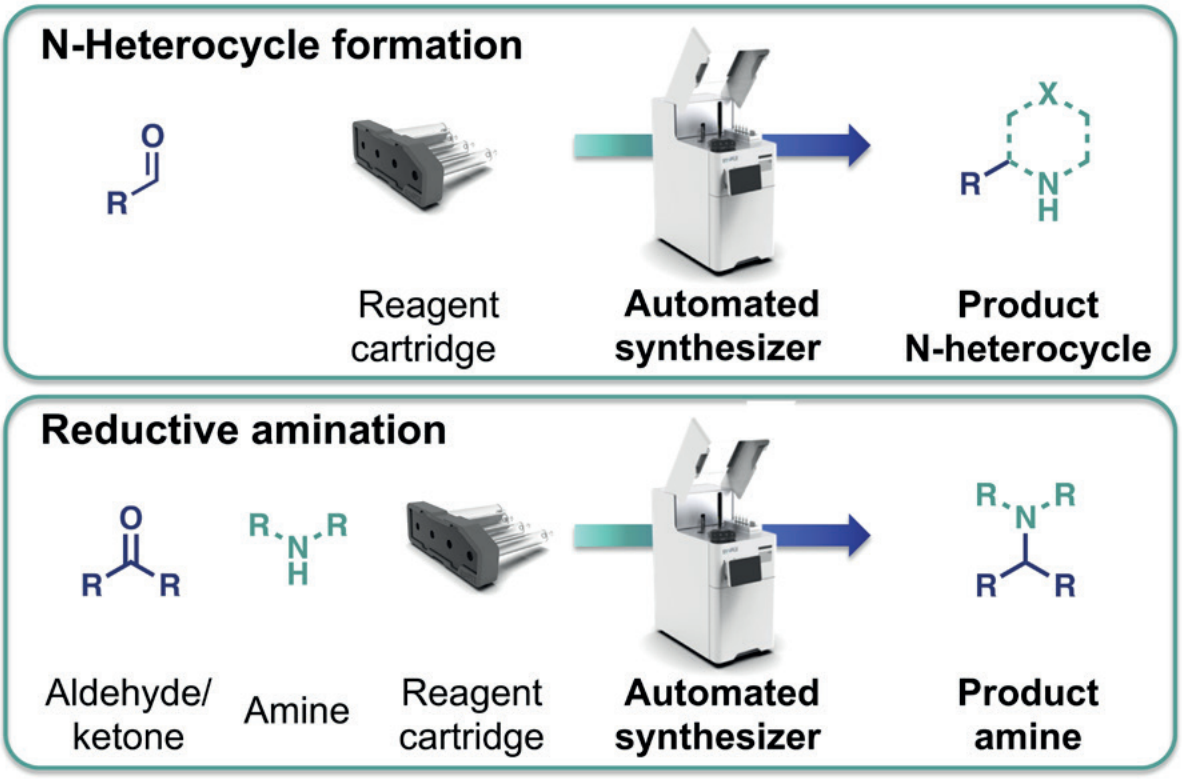
Automation in synthetic organic chemistry is highly desirable due to improved safety, reproducibility and the productivity enhancing benefits. However, despite significant advances in the field, very few truly “plug and play” systems exist that combine both convenience and reliability with ease of use. With this goal in mind, an innovative, integrated, capsule-based, fully automated console has been developed for executing organic synthesis.



The utility of this automated technology is demonstrated for the formation of saturated N-heterocycles, reductive aminations, and multistep combinations, which enable rapid and highly efficient the preparation of complex drug-like molecules.

CHEMISTRY AND BIOLOGY OF INTERVENOLIN ANALOGS: ANTIPROLIFERATIVE AND ANTI-HELICOBACTER PYLORI ACTIVITIES

Takumi Watanabe (1), Hikaru Abe (1), Manabu Kawada (1,2), Chiharu Sakashita (1), Shun-ichi Ohba (2), Hiroyuki Inoue (2), Tomokazu Ohishi (2), Tohru Masuda (2), Chigusa Hayashi (1), Masayuki Igarashi (1), Masakatsu Shibasaki (1)

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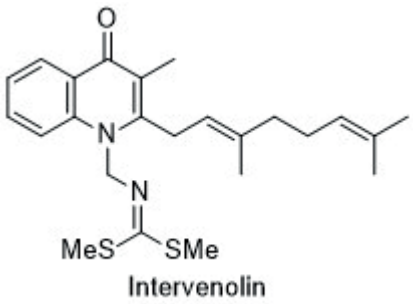
Targeted therapy is very successful. Therapeutic agents with a tumor-specific molecular target are expected to be inert to normal tissues and have low toxicity. Compared with the genes in normal cells, those in tumor cells are more prone to mutation, leading to frequent emergence of resistance.

We are interested in growth signals emitted from stromal cells that affect the fate of tumor cells in tumor tissue (tumor–stroma interaction). A screening campaign to search for modulators of the tumor–stroma interaction revealed a novel natural product originating from the microorganism intervenolin as a hit compound able to more potently inhibit the growth of tumor cells cocultured with the corresponding stromal cells than under monocultured conditions.[1]

Intervenolin has a 4-quinolone chromophore with substitutents at the 1-position, a pendant iminodithiocarbonate substructure, and a geranyl side chain at the 2-position. We established a synthetic route to intervenolin,[2] which has accelerated structure-activity relationship studies to realize substantial enhancement of the cocultured condition-selective antiproliferative activity without noticeable acute toxicity in mice.[3]

Interestingly, anti-*Helicobacter pylori* activity comparable to that of a positive control, clarithromycin, was observed for some of the analogs with remarkable selectivity over other species of microorganisms.[3] One analog exhibited superior therapeutic efficacy in an in vivo standard “triple therapy” regimen.[4]



Intervenolin

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SYNTHESIS OF NEW LIGANDS FOR BITTER TASTE RECEPTOR TAS2R14

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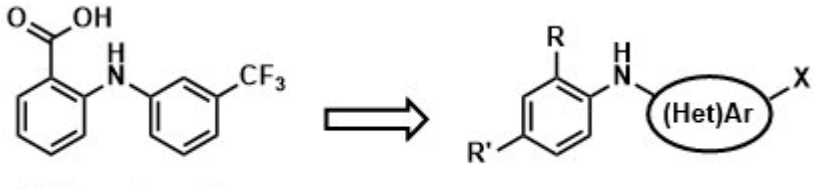
The perception of bitterness is of particular importance in order to prevent the unintentional uptake of toxic food components that often have bitter taste.[1] Responsible for the perception of bitter taste is are taste receptors of type 2 (TAS2Rs) belonging to the large family of G protein-coupled receptors (GPCRs).[2] Intriguingly, TAS2Rs are also expressed in extra-oral tissues, such as human airway smooth muscle and the heart, making them a potential novel drug target.[3,4] TAS2R14 is one of the most broadly investigated taste receptor, as it is activated by natural and synthetic compounds which vary greatly in their structure.[5]



flufenamic acid

In this work, flufenamic acid, one of the most potent and selective agonists for TAS2R14[1], served as a lead structure for the design and synthesis of new derivatives. Using methods of computational docking and bioisosteric exchange, we intend to gain further information on the binding pocket of TAS2R14. *In vitro* testing of the synthesized molecules revealed a few compounds with similar or higher potency compared to the reference agent. The studies including 5-substituted tetrazoles as a new compound family binding and activating the receptor. 5-Substituted tetrazoles served as a useful structural elements replacing the carboxylic acid function of the lead compound.

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DEVELOPMENT OF SMALL MOLECULE NOTUM INHIBITORS TO POTENTIATE WNT SIGNALLING

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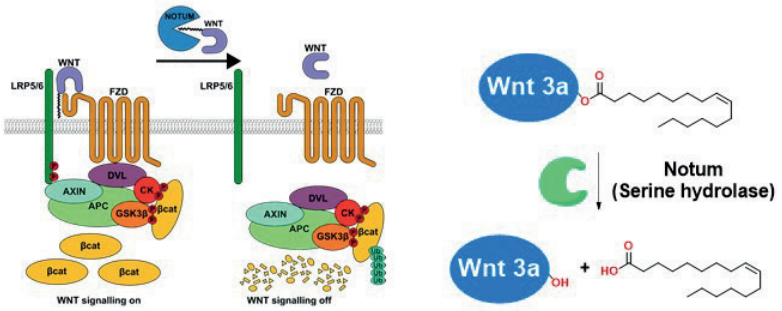
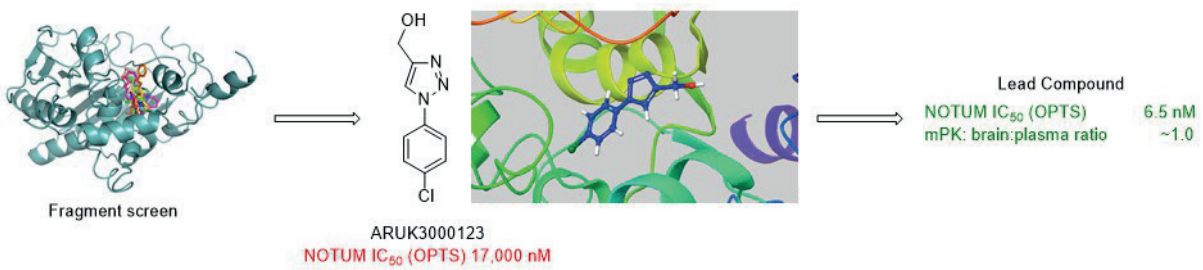
Dysfunctional Wnt signalling has been associated with a variety of pathologies, including neurodegenerative diseases such as Alzheimer's disease (AD). The Wnt family is comprised of 19 secreted proteins and the Wnt pathway itself is regulated by a range of mechanisms including post translational modifications (PTMs). *O*-Palmitoleoylation of Wnt proteins is a key PTM required for efficient binding of Wnt proteins to Frizzled (Fzd) receptors, a requirement for signal transduction.[1]



The serine hydrolase Notum has been shown to suppress Wnt signalling pathways by mediating the depalmitoleoylation of Wnt proteins.[2] Therefore, inhibition of Notum by small molecule modulators could enhance Wnt signalling, providing potential therapeutic benefit in AD.

Using an X-ray fragment screening approach to identify novel CNS penetrant inhibitors of Notum, 60 compounds were found to bind within the palmitoleoyl pocket. From these hit compounds a series of aryl triazoles was identified and SAR developed further using structure based drug design approaches, resulting in lead compounds showing single digit nanomolar potencies in our biochemical assay and excellent CNS penetration.



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SYNTHESIS AND APPLICATIONS OF NOVEL FLUOROBENZOIODAZOLONES

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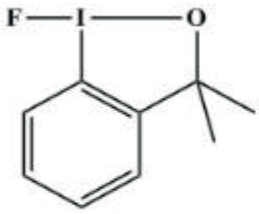
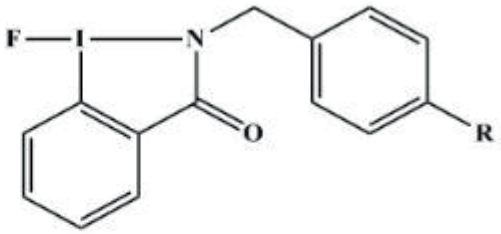
There has been considerable interest in recent years in the applications of fluoroiodane (A) as a versatile, shelf-stable fluorinating reagent.[1-3] We have been interested in synthesizing alternative fluorinated hypervalent iodine(III) reagents in order to: (i) control the fluorinating activity and (ii) simplify the synthetic methodology. Here, we report the synthesis, structures and reactivity of a series of benzyl-substituted fluoroiodazolones (B) incorporating a novel fluorine-*trans*-nitrogen iodine(III) structural unit.



(A)



(B)

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DEVELOPMENT OF GSTO1-1 INHIBITORS FOR THE TREATMENT OF INFLAMMATORY CONDITIONS

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Glutathione transferase omega 1-1 (GSTO1-1) is an enzyme which has recently been shown to have an essential role in bacterial lipopolysaccharide (LPS) stimulated inflammatory responses,[1] as well as to mediate the activation of NLRP3 inflammasome by deglutathionylating NEK7.[2] The inhibition of this enzyme could potentially target various diseases, including acute and life-threatening inflammatory responses such as those involved in sepsis, NLRP3 inflammasome involved diseases such as type 2 diabetes and Alzheimer's disease, and diverse human cancers.[3] So far, a diverse array of small molecules have been reported as GSTO1-1 inhibitors, although they are all relatively underdeveloped.[3] The most extensively investigated inhibitors were discovered as activity-based probes, which function by covalently labeling the active site GSTO1-1 cysteine (Cys32) thiol with their chloroacetamide warheads.[4,5] In this work, we chose one of these chloroacetamides, termed C1-27, as the lead compound for medicinal chemistry optimization towards novel GSTO1-1 inhibitors with better inhibitory activity. We researched the potential for decreasing ligand reactivity, as well as using structure-guided design aimed to increase non-covalent interactions, in order to improve the chances of selectivity and safety while maintaining potency. In the work to be presented, we investigated the lead-likeness of C1-27 in depth, synthesized three series of novel C1-27 analogues to study its structure-activity relationship (SAR) and evaluated their enzymatic inhibitory activities by 4-NPG assay. The k_{inact}/K_I values of selected compounds were measured as a more accurate potency evaluation of covalent inhibitors. We also tested the inhibitory activities of selected compounds in cell.

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DISCOVERY OF NOVEL QUINAZOLINE-2,4(1H,3H)-DIONE DERIVATIVES AS PARP-1/2 INHIBITORS WITH ANTI-CANCER ACTIVITY

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Poly(ADP-ribose) polymerase-1/2 (PARP-1/2) played a key role in DNA breaks repair and have been extensively studied as targets for cancer treatments in preclinical and clinical models[1,2]. Both of them catalyzed the cleavage of nicotinamide adenine dinucleotides (NAD^+) into nicotinamide and ADP-ribose units, which were transferred to proteins participating in DNA damage repair processes including histone and PARP-1/2 and formed ADP-ribose polymers (PAR). It has been demonstrated that PARP-1/2 inhibitors were useful for the treatment of cancers either as a single agent or in the combination therapy. In fact, Olaparib (AZD-2281), Rucaparib (AG014699), Niraparib (MK4827) and Talazoparib (BMN673) have been approved by FDA for the treatment of ovarian cancer in patients with or without BRCA mutations during the period of 2014-2018.

A series of novel 1-substituted benzyl-quinazoline-2,4(1H,3H)-dione derivatives as PARP-1/2 inhibitors were designed and synthesized. Two compounds (**A** IC_{50} = 0.51 nM/23.11 nM, and **B** IC_{50} = 1.31 nM/15.63 nM) were identified as the most potent PARP-1/2 inhibitors in this work. The inhibitory activity against PARP1/2 on the cellular level was evaluated and they can inhibit the PAR formation significantly. The in vivo antitumor activity of these two compounds as sensitizer was evaluated using U87MG/Luc glioma tumor model. Compared with the TMZ (30 mg/Kg) treated group, the combination therapy group (30 mg/Kg TMZ + 50 mg/Kg compound A) displayed pronounced antitumor activity with the tumor growth inhibition of 85.9%, and the combination treatment with compound B produced even more remarkable efficacy with TGI of 99.8%. The X-ray crystal structure of compound C complexed with PARP-1 was disclosed and the binding features of this series of compounds were analyzed.

In summary, novel quinazoline-2,4(1*H*,3*H*)-dione derivatives were obtained as PARP1/2 inhibitors with high potency. Compound B was found to be a potent antitumor agent for the treatment of glioma.

Acknowledgement

This work is supported by National Natural Science Foundation (No. 81673300), National Science & Technology Major Project “Key New Drug Creation and Manufacturing Program”, China (2018ZX09711001) and CAMS Initiative for Innovative Medicine (CAMS-I2M-2-004).

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ACOUSTIC DROPLET EJECTION ACCELERATED HIT IDENTIFICATION TARGETING ON MENIN PROTEIN

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Automated, miniaturized and accelerated synthesis for efficient property optimization and fast compounds screening in chemical and pharmaceutical research are critically important. Here, we used the acoustic droplet ejection (ADE) technology and fast quality control to generate a library of potential candidates targeting on Menin protein. With ADE technology, the machine only transferred building blocks by nL droplets and scouted new compounds in a fast speed. Combining this technique with powerful multi-component reaction (MCR) leads to the possibility to perform organic synthesis in a low material-consuming and time-saving way. Totally, four 386-plates were generated and around 50% reactions succeed with a high quality. Then the plated were used for screening against Menin protein, and around 20 potential hits were found. All these potential candidates were resynthesized in a mmol scale and were tested again the binding possibility to Menin protein. Finally, several hits were found. Miniaturization and analysis of the generated big synthesis data enabled deeper exploration of the chemical space. Large designed library which is generated by ADE technology and MCR can be used for high-throughput screening. Thus, ADE technology together with MCR leads to accelerate hit identification for drug discovery to a large extent.

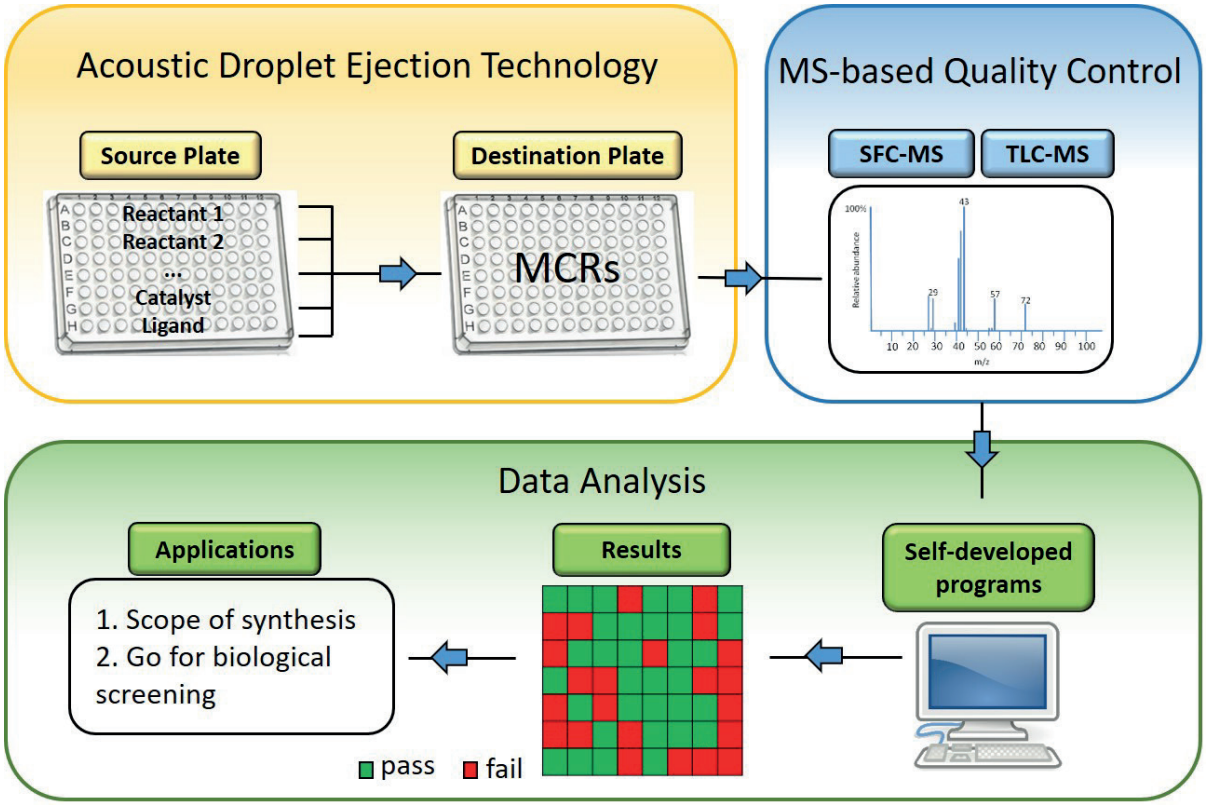

Figure 1. Workflow of acoustic dispensing-enabled reaction scouting

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW BENZOTHIAZOLE AMIDE DERIVATIVES AS BRAFV600E INHIBITORS

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BRAF mutations are present in 8% of human cancers and they appear in different malignant tumors, more frequently in melanoma (>50%).[1] So far, two selective BRAF inhibitors have been approved by the FDA for the treatment of metastatic melanoma with BRAFV600E mutation and also combination therapy with MEK inhibitors.[2] However, due to the rapid development of resistance to treatment and the various side effects that come along with therapy, the interest in this field has focused in the discovery of new inhibitors of the MAPK pathway that overcome the problems mentioned above. In order to contribute in this field, we designed and synthesized a series of compounds using the benzothiazole ring as a scaffold, a functional group that is present in many approved drugs (Figure 1). In the present study, we describe the synthesis of novel benzothiazole derivatives containing side chains with amide, sulfonamide or other groups. Synthetic schemes as well as biological evaluation of the target molecules will be discussed.

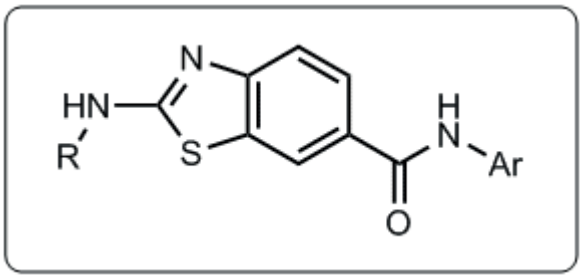

Figure 1: General structure of new benzothiazole derivatives.

Acknowledgements

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Also, we acknowledge support of this work by the project “STHENOS-b: Targeted therapeutic approaches against degenerative diseases with special focus on cancer and ageing-optimisation of the targeted bioactive molecules” (MIS 5002398).

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DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NOVEL AMINOPYRIMIDINYLCARBOXAMIDES AS AXL AND ACK1 INHIBITORS

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AXL is a receptor tyrosine kinase involved in the growth, differentiation, survival, and motility of many different cell types. AXL has been correlated with poor survival in numerous aggressive tumours including TNBC, AML, NSCLC, pancreatic cancer, and ovarian cancer. The emergence of ACK1 has uncovered novel mechanisms by which tyrosine kinase signalling promotes cancer progression. The ACK1 tyrosine kinase is aberrantly activated, amplified, or mutated in many types of human cancers, including prostate, breast, pancreatic, ovarian, and lung cancers. Therefore, AXL and ACK1 have been proposed as the attractive targets for cancer therapeutics and a number of small molecule inhibitors have been developed.

Many kinase inhibitors utilize the pyrimidine scaffold as a hinge anchor with various substitutions at 2- and 4-positions. In this work, a novel series of aminopyrimidine derivatives, based on the structural features of TP-0903 and TAE-684 as AXL and ACK1 inhibitors, were designed and synthesized. Among them, several compounds showed potent inhibitory activities against AXL and ACK1 with IC_{50} values of sub-micromolar range, respectively. Their *in vitro* antiproliferative activities were tested over three cancer cell lines. Most compounds showed good antiproliferative activities against MV4-11 cell. In our series, compound **1q** possessing phenylaminophenyl moiety exhibited best combination against AXL, ACK1, and MV4-11. It can be used as a promising lead for the development of potent AXL and ACK1 kinase inhibitors.

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COMPUTER-AIDED DESIGN, SYNTHESIS AND ENZYMATIC ANALYSIS OF NEW TRIAZOLE DERIVATIVES AS POTENTIAL FACTOR Xa INHIBITORS

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The World Health Organization (WHO) reported that thrombosis diseases had increased their cases up to 25 % of people. Relevant diseases in thrombosis pathology include acute coronary syndrome (ACS), venous thromboembolism (VTE), deep vein thrombosis (DVT); all of them caused by clots; this can trigger strokes whose travel through arterial circulation. Giving rise to serious diseases like acute myocardial infarction (AMI) [1]. Factor Xa (FXa) plays a key role in haemostasis, due to it is a central part of the blood coagulation cascade which catalyzes the production of thrombin and leads to clot formation and wound closure. Clotting is a sequential process that involves the interaction of coagulation factors [2]. Inhibition of FXa should prevent the production of new thrombin without affecting its basal level, ensuring primary haemostasis, unlike injectable heparins or the most commonly used oral anticoagulant in the US, such as warfarin.

In this research novel aryl azides were synthesized incorporating a lactamic ring with different heteroatoms in position 4 as starting materials. A variety of 1,2,3-triazoles were prepared using copper nanoparticles as catalyst (10 mol %) from different aryl azides synthesized in the first microwave synthesis step [3-4]. The products of interest were obtained in good to excellent yields (70-97%). By using computational tools allows us to develop new synthetic ligands to interact with high specificity with the S1 and S4 pockets enzyme. The aryl lactam core shows favorable π- π interactions with the S4 pocket (Figure 1). Moreover, FXa inhibition assays were performed in order to obtain the IC_{50} values of the corresponding new derivatives [5].

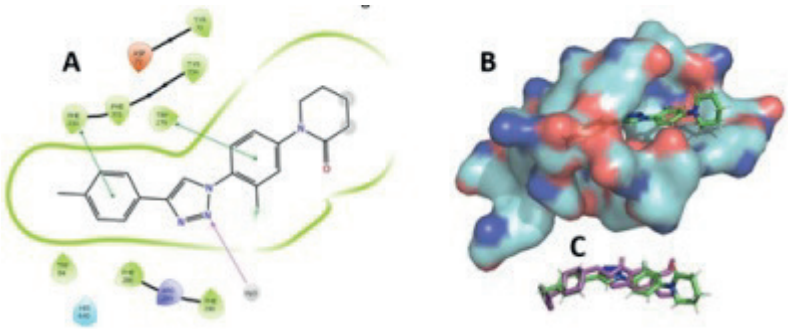

Figure 1. Molecular coupling analysis for the most active derivative. **(A)** Diagram of interactions in the active site. **(B)** Enzyme-ligand complex. **(C)** Superposition of standard ligand and the most active derivative.

Acknowledgements: FS-R thaks to Beca VRI-Instructor Becario UC 2019. FZ is greatful to Project Conicyt-Fondecyt N° 1181408.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW FLUORINATED LIGANDS TARGETING P2XR

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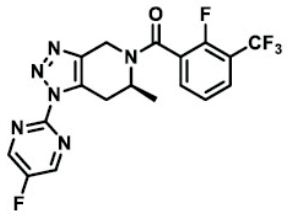
The central nervous system (CNS) is the part of the nervous system consisting of the brain and spinal cord. Neurodegenerative diseases as Parkinson's, Alzheimer's or epilepsy are typically associated with chronic inflammation of the CNS - neuroinflammation. It is a part of the complex biological response of body tissues to pathogens or damaged cells. The function of inflammation is to eliminate the initial cause of cell injury and initiate tissue repair. The initial microglial response that occurs in neuroinflammation is characterized by microglial accumulation in the injured sites of the brain (1).

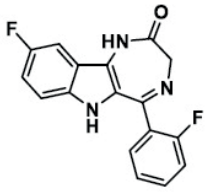
Inflammatory conditions are associated with the extracellular release of nucleotides, particularly ATP. Extracellular ATP is activated by ionotropic P2X receptors. Among seven members of P2XR family, P2X7 is expressed by a variety of cells type in brine as neurons and microglial cells. Although several other P2XRs are functional during inflammation, P2X7R, in particular, has been shown to affect the outcomes of inflammatory or infectious diseases (2).

Similar receptor P2X4 may also act as an initial trigger of neuroinflammation. It forms a large conductance pore on the cell membrane, facilitating ion efflux and subsequent inflammasome activation (3).

In the literature, there are few described references targeting those two receptors (Fig. 1.). Based on literature research, we designed and synthesized new scaffolds and a series of original fluorinated compounds. The activity of all the molecules was evaluated. The most promising ligands will become a potential ^{18}F probes to early diagnosis CNS disorders.



$P2X_7$ IC_{50} = 5,9 nM
Janssen Pharmaceutical NV



$P2X_4$ IC_{50} <100 nM
Sunovion Pharmaceuticals Inc.

Fig. 1. Reference molecules

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A NOVEL CLASS OF SPECIFIC CK2 INHIBITORS TARGETING ITS OPEN HINGE CONFORMATION

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In this work we developed a new class of CK2 inhibitors, a protein kinase considered a valuable pharmacological target in several cancers, especially in hematological malignancies[1]. These new chemical entities are particularly interesting due to their ability to interact with the CK2 open hinge conformation, an extremely rare feature among kinases inhibitors. The synthesis of our class of compounds started from a well-known and specific inhibitor of CK2: SRPIN803[2]. Its chemical structure is based on a 6-methylene-5-imino-1,3,4-thiadiazolopyrimidin-7-one scaffold. Our synthesis of SRPIN803 resulted in compound **1**, where the 2-cyano-2-propenamide group does not cyclise and fuse to the thiadiazole ring. Its crystallographic structure in complex with CK2 identifies the structural determinants of the reported specificity. The optimization of compound **1** led to the more potent compound **4**, which inhibits endocellular CK2, significantly affects viability of Jurkat cells and shows remarkable specificity on a panel of 320 kinases.

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OXINDOLE SYNTHESIS VIA ORGANOCATALYTIC REACTIONS WITH THIOESTER ENOLATES

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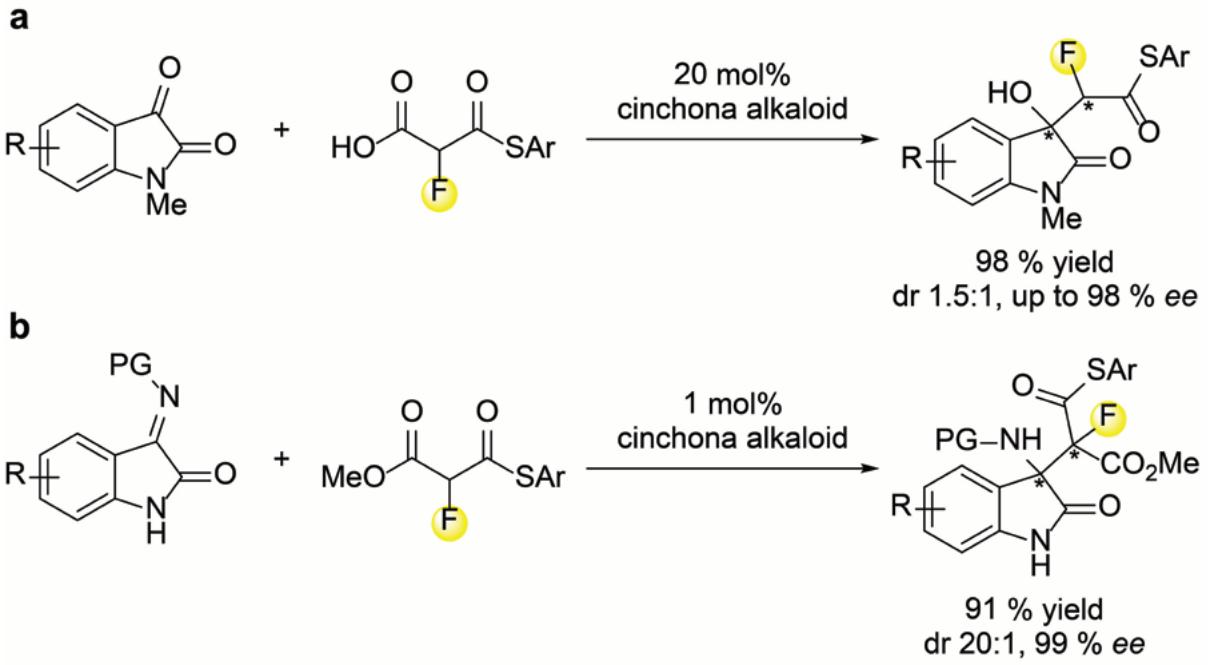
Thioester enolate surrogates are utilized by nature for the synthesis of polyketides or fatty acids[1] and are valuable in organic chemistry for C-C bond formations.[2] Our group developed alkylated and fluorinated malonic acid half thioesters (MAHTs) and monothiomalonates (MTMs) as masked thioester enolate equivalents and used them in organocatalytic addition reactions to several electrophiles, including nitroolefins, imines, isatin-ketimines and aldehydes. The products were obtained in excellent yields and stereoselectivities.[3]

We are currently expanding this methodology to reactions of fluorinated thioester enolate equivalents with isatins and isatin-ketimines to access fluorinated oxindoles. Oxindoles are prominent motifs in many therapeutically active compounds[4] and fluorine substituents can be expected to further enhance their potency.[5]

Fluorinated malonic acid half thioesters (F-MAHTs) undergo decarboxylative addition to protected isatins using cinchona alkaloid catalysts in excellent yields and moderate to excellent stereoselectivities (Scheme 1a).

The addition of fluorinated monothiomalonates (F-MTMs) to isatin-ketimines using cinchona alkaloids as catalysts, provided 3-amino oxindoles in excellent yields and stereoselectivities (Scheme 1b). Remarkably low catalyst loadings and short reaction times sufficed to obtain the product with two adjacent tetrasubstituted stereocenters without the need for a protecting group at the isatin lactam.

The poster will present the scope of the organocatalytic reactions and the preparation of downstream analogs of the chiral 3-hydroxy and 3-amino oxindoles.



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DISCOVERY SELECTIVE AND POTENT ASPARTATE TRANSCARBAMOYLASE (ATCASE) INHIBITORS

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Aspartate transcarbamoylase catalyzes the second step of de-novo pyrimidine biosynthesis. As malarial parasites lack pyrimidine salvage machinery and rely on de-novo production for growth and proliferation, this pathway is a target for drug discovery. Previously, an apo crystal structure of aspartate trans-carbamoylase from Plasmodium falciparum (PfATC) in its T-state has been reported. Here we present crystal structures of PfATC in the liganded R-state as well as in complex with the novel inhibitor, BDA-05, identified by mixture screening. Our data shows that the inhibitors bind sin close proximity to the active site and a new pocket, implying an allosteric mechanism of inhibition. Furthermore, we found some selective and potent inhibitors, the K_d = 50 nM. These data provide a promising starting point for structure based drug design targeting PfATC and malarial de-novo pyrimidine biosynthesis.

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DEVELOPMENT OF L-741,626 ANALOGUES SELECTIVELY TARGETING THE DOPAMINE D2 RECEPTOR

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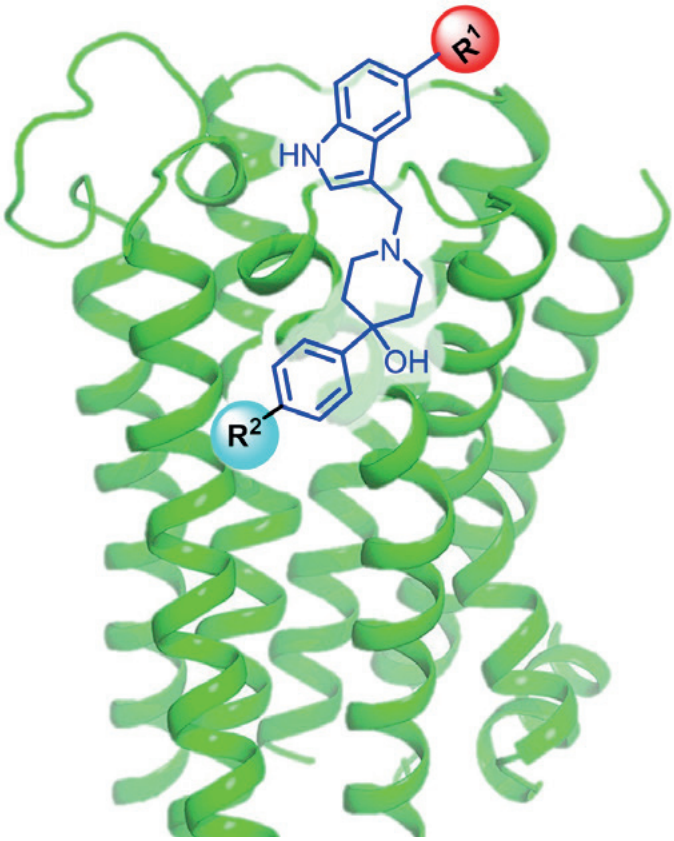
Dopamine receptors belong to the 'Class A' rhodopsin family of G protein-coupled receptors (GPCRs) and are essential for many neurological processes. Among the five dopamine receptor subtypes, the dopamine D_2 receptor (D_2R) is a crucial target for treating schizophrenia and Parkinson's disease. However, despite the evident therapeutic importance, there is a scarcity of highly selective compounds targeting D_2R.

The antagonist L-741,626 displays selectivity for the D_2R over the structurally related dopamine D_3 receptor (D_3 R) and dopamine D_4 receptor (D_4R) subtypes.[1-2] This pattern of subtype selectivity is distinct from the majority of ligands designed to target the D_2-like dopamine receptors that do not display selectivity across this receptor family. In this research, we aimed to design and synthesize a focused library of L-741,626 analogues and study their binding mode to the D_2R, to develop ligands with enhanced receptor selectivity as a potential treatment for schizophrenia. Additionally, this research could provide a source of new pharmacological tools for exploring the structure and physiological role of the D_2R. We successfully synthesized and pharmacologically characterized several rationally designed L-741,626 analogues. Some of these compounds are able to bind to D_2R with high affinity and selectivity over the highly homologous D_3R and D_4R subtypes. These results provide insights into the binding directions of this important compound.



NOVEL SELECTIVE ESTROGEN RECEPTOR DEGRADERS (SERDs) WITH DIFFERENT DEGRONS DISPLAYING ENHANCED ER DEGRADATION ACTIVITY

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As the mutant estrogen receptor (ER) continues to be characterized, breast cancer is becoming increasingly difficult to cure when treated with hormone therapy.[1] In this regard, a strategy to selectively and effectively degrade the ER might be an effective alternative to endocrine therapy for breast cancer. In a previous study, we identified a novel series of 7-oxabicyclo[2.2.1]heptene sulfonamide (**OBHSA**) compounds as full ER antagonists while lacking the prototypical ligand side chain that has been widely used to induce antagonism of ERα.[2] Further crystal structure studies and phenotypic assays revealed that these compounds are selective estrogen receptor degraders (SERDs) with a new mechanism of action.[3] However, from a drug discovery point of view, there still is room to improve the potency of these **OBHSA** compounds. In this presentation, we will describe new classes of SERDs that contain the **OBHSA** core structure and different side chains, e.g., basic side chains, long alkyl acid side chains, and glycerol ether side chains, to simply mimic the degrons of proteolysis targeting chimera (PROTAC) and then investigated the structure-activity relationships of these PROTAC-like hybrid compounds. These novel SERDs could effectively inhibit MCF-7 cell proliferation and demonstrated good ERα degradation efficacy. Among the SERDs, compounds containing a basic side chain with a *N*-trifluoroethyl substituent and a *para* methoxyl group at the phenyl group of the sulfonamide turned out to be the best candidates for ER degraders. A further docking study of these compounds with ERα elucidates their structure-activity relationships, which provides guidance to design new PROTAC degrons targeting ER for breast cancer therapy. Lastly, easy modification of these PROTAC-like SERDs enables further fine-tuning of their pharmacokinetic properties, including oral availability.

Acknowledgements:

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NEW 2,6-DISUBSTITUTED THIOSEMICARBAZIDE DERIVATIVES OF PYRAZINE WITH ANTIMICROBIAL ACTIVITY

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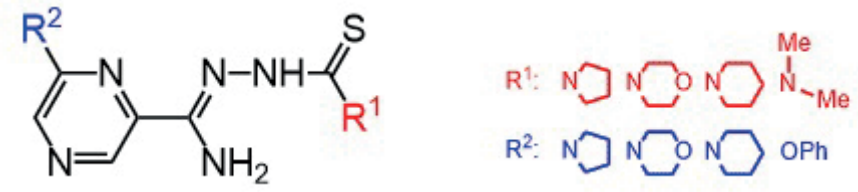
Tuberculosis is one of the first infectious diseases with an identified bacterial pathogen called *Mycobacterium tuberculosis* [1]. The urgent need to develop new active agents to combat tuberculosis has been caused by the emergence of multidrug and extensively drug-resistant strains of *M. tuberculosis* and the necessity of the use of combination drug therapy. Intensifying the search for new drug is one of the pillars of the World Health Organization's End TB Strategy which aims to end the global TB epidemic by 2035 [2].

Previously we described an interesting tuberculostatic activity of some compounds bearing pyrazine and pyridine heterocyclic rings [3,4]. Our interest in that research field resulted from the presence of these structural elements in molecules of registered anti-tuberculosis chemotherapeutics, e.g. pyrazinamide (PZA) and isoniazid (INH). Extensive structure-activity relationship research for hitherto obtained compounds revealed that thiosemicarbazide derivatives contained pyridine and pyrazine ring and cycloalkylamine ring in the thiosemicarbazide chain have higher antitubercular activity than INH. Here we disclose the synthesis of novel disubstituted thiosemicarbazide derivatives of pyrazine as structural analogues of active compounds presented previously.

The starting substrate for the synthesis of twenty novel derivatives (Figure) was 2-cyano-6-chloropyrazine. Nitrile functional group was converted into methyl imidate group. Methyl imidates underwent the reaction with various cycloalkylamino-1-carbothiohydrazines and N,N-dimethylaminocarbothiohydrazine giving cycloalkylaminocarbothiosemicarbazide derivatives and N,N-dimethylaminocarbothiosemicarbazide derivative. In the next step chlorine atom in starting compound was substituted by morpholine, piperidine, pyrrolidine and phenoxy moiety in nucleophilic reaction. In this instance, corresponding derivatives were obtained directly from the nitrile while treated with various aminocarbothiohydrazines.



All the newly synthesized compounds were characterized by IR and ^{1}H NMR spectra. Obtained derivatives of 2-cyano-6-chloropyrazine were evaluated for their *in vitro* tuberculostatic activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain and two clinical strains isolated from tuberculosis patients: one (Spec. 210) resistant to, inter alia, INH and the another (Spec. 192) fully sensitive to the administered tuberculostatics. They were also screened for antibacterial and antifungal activities. Minimal inhibitory concentration (MIC) of the tested derivatives were evaluated for the panel of the reference microorganisms from American Type Culture Collection, including Gram-negative bacteria, Gram-positive bacteria and fungi. The tested derivatives showed differential, quite interesting, tuberculostatic and antibacterial activity.

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INVESTIGATION OF FLEXIBILITY OF NEURAMINIDASE 150-LOOP USING TAMIFLU DERIVATIVES IN INFLUENZA A VIRUSES H1N1 AND H5N1

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Treatment of Influenza with oseltamivir and zanamivir targets key surface glycoprotein neuraminidase. Clinical studies of isolated influenza strains H5N1, H1N1 showed increasing resistance towards mentioned inhibitors.[1,2]

This study focuses on design, synthesis and in vitro evaluation of inhibitory potency of two series of oseltamivir derivatives that target an exosite ("150-cavity") adjacent to the active site of influenza neuraminidases from A/California/07/2009 (H1N1) pandemic strain and A/chicken/Nakorn-Patom/Thailand/CU-K2-2004 (H5N1). The structure-activity analysis as well as 3D structure of the complex of parental compound with the pandemic neuraminidase p09N1 revealed high flexibility of the 150-cavity towards various modification of the neuraminidase inhibitors. Furthermore, the two methods for inhibition constant determination performed at different pH values provided us with two sets of results. The results will be discussed.[3]

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SYNTHESIS, PHOTOCHEMICAL REACTIVITY AND BIOLOGICAL ACTIVITY OF QUINONE METHIDE PRECURSORS CONTAINING BODIPY CHROMOPHORE - POTENTIAL ANTICANCER DRUGS

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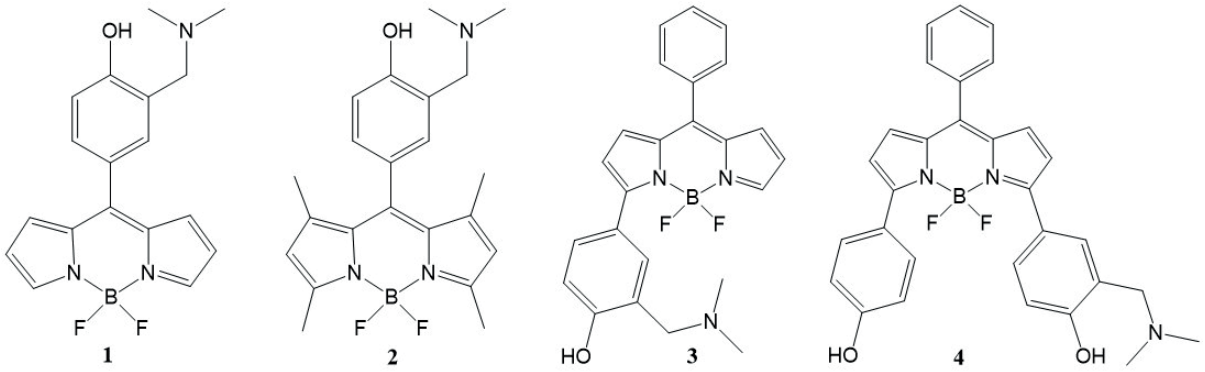
Quinone methides (QMs) are reactive intermediates that have been shown as useful synthons in organic synthesis,1 as well as biologically active agents applicable in biochemistry and medicine.[1,2]

It has been shown that QMs react with nucleotides and induce DNA alkylation and cross-linking, leading to cytotoxicity.[3-5] The generation of QMs under mild conditions can be facilitated by photochemical elimination reactions.[6] On the other hand, BODIPY derivates are commonly used dyes for biomolecular labeling since they are characterized by good photochemical stability and excellent photophysical and spectral properties.[7]

To obtain molecules which can be excited by visible light of >650 nm which is needed for the penetration through tissue, we incorporated BODIPY chromophore into the QM precursor units.[8]

BODIPY-QM precursor molecules **1-4** have been synthesized in the multi step synthetic pathway that includes condensation of an aldehyde and pyrrole to dipyrromethane moiety, its transformation to the BODIPY chromophore and subsequent functionalization. For **1** and **2**, the target molecules were obtained in a Mannich reaction. On the other hand, **3** and **4** were prepared in a reaction sequence involving chlorination with N-chlorosuccinimide, Suzuki coupling, deprotection of the benzyl group from the phenol and the Mannich reaction. Synthesized precursor molecules **1-4** undergoe photodeamination reactions and deliver the corresponding QMs that react with nucleophiles in a Michael addition, which may lead to biological effects. Antiproliferative activity of synthesized BODIPY-QM precursors was investigated using MTT assay on several cell lines with and without irradiation. An enhancement of the activity was observed for the cells that were irradiated. The MTT results will be discussed in light of the photochemical reactivity of the molecules and some structure-photoreactivity-biological activity relationship will be demonstrated.



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METAL CHELATORS AGAINST VIRUSES

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Influenza viruses cause considerable morbidity and mortality, whether in the context of annual epidemics, sporadic pandemics, or outbreaks of avian influenza virus. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections pose a major public health threat globally, with the infected people being at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. It is noteworthy that the worldwide mortality associated with liver cancer and cirrhosis has increased over the last decades. Moreover, the flaviviruses Dengue (DENV), Yellow fever (YFV) and West Nile (WNV) are high priority targets for drug discovery as they are reemerging global pathogens with no clinically approved specific therapy (WHO). Since emerging viral resistance remains high, the cost threaten the efficacy of currently approved antiviral drugs and the attention of pharmaceutical industry concerning neglected and relatively unprofitable virus disease is little, new antiviral drugs are urgently needed.

Approximately one-third of proteins are metalloproteins, some of them are responsible for a wide variety of essential viral functions in vivo. Pathologies for which metalloenzymes are implicated include influenza A and HCV. Given the impact of these infectious diseases on human health, metalloenzyme inhibition offers an appealing approach to disease treatment. Hydroxamates act as bidentate ligands and are able to form hydrogen bonds; they can act as potent inhibitors of any enzyme that contains metal ion and residues able to act as hydrogen-bond donors or acceptors. Almost all the enzymes that contain M^{2+} ion are easily coordinated with any hydroxamic acid derivative. Thus, the metal-chelating property and multiple hydrogen-bond formation ability of hydroxamates have made them a novel and intriguing antiviral class of compounds.

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DESIGN, CHEMICAL SYNTHESIS AND FUNCTIONAL CHARACTERIZATION OF NOVEL AGENTS TARGETING PERSISTER AND PATHOGENIC BACTERIA

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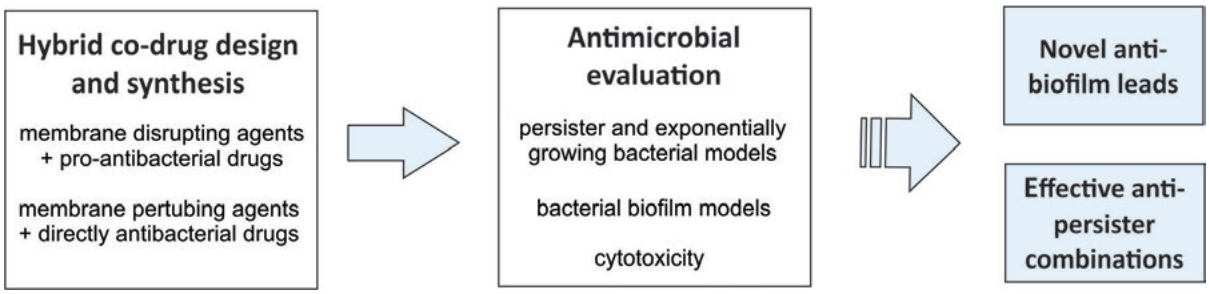
Antimicrobial resistance is a major global threat for public health and it is associated with soaring treatment and extensive societal costs. Infections caused by antibiotic-tolerant, biofilm forming Gram-negative bacteria, such as *P. aeruginosa*, are alarmingly rising and increasingly dependent on the use of last-resort drugs, such as colistin, which have also encountered evolving resistance [1]. On the other hand, the multidrug-resistant, biofilm-forming Gram-positive *S. aureus*, the causative species of various hospital-associated infections, is of especially serious concern. It has been now demonstrated that a bacterial phenotype known as "persister cells" exists, consisting of specialized survivor cells which cannot be eliminated by antibiotic therapy [2]. Studies of dose-dependent killing of *P. aeruginosa* biofilm have shown the presence of a small subpopulation of bacterial cells completely tolerant to antibiotics such as ofloxacin and ciprofloxacin [3]. The currently existing antimicrobial drugs possess only limited activity, if any, against persister cells. Thus, after a typical course with antibiotics, persister cells remain unaffected and they can switch into a metabolically active state as soon as the antimicrobial therapy is terminated, thus prompting the relapse of the infection and prolonged treatment periods [4].

The aim of the project is to design, synthesize and evaluate novel compounds against persister and rapidly multiplying pathogens of *S. aureus* and *P. aeruginosa*. Several antimicrobial co-drugs of membrane disrupting agents, pro-antibacterial and directly antibacterial drugs can be designed and synthesized, as indicated in the scheme below. Successfully synthesized compounds will be evaluated for their antimicrobial activity to determine their effect on persister and exponentially growing bacteria, bacterial biofilms and their use in the protection of clinically relevant biomaterials. Cytotoxicity of the selected drugs will be determined in mammalian cell lines as well.



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MC3353 - A PROMISING QUINOLINE-BASED DNA DEMETHYLATING COMPOUND HIGHLY POTENT IN CANCER CELLS

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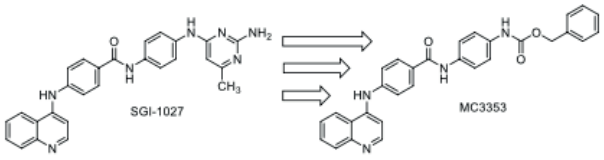
Background: DNA methyltransferases (DNMTs) are epigenetic enzymes involved in embryonic development, cell differentiation, epithelial to mesenchymal transition and control of gene expression, whose overexpression or enhanced catalytic activity has been widely reported in cancer initiation and progression.[1] To date, two DNMT inhibitors (DNMTi), 5-azacytidine (5-AZA) and 5-aza-2'- deoxycytidine (DAC), are approved for treatment of myelodysplastic syndromes and acute myeloid leukemia. Nevertheless, they are chemically instable and quite toxic for healthy cells, thus the discovery of novel DNMTi is urgent. [1,2]



Scheme1: Design of MC3353

Results: We will present the identification of a new quinoline-based molecule, MC3353, as a non- nucleoside inhibitor and downregulator of DNMT. The design of MC3353 is based on the known non nucleosidic DNMTi SGI-1027 replacing the 4-methyl-2,6-diaminopyrimidine moiety of the template with a benzyl carbamate function. This compound was able, in promoter demethylating assays, to induce enhanced green fluorescence protein (EGFP) gene expression in HCT116 cells and transcription in a cytomegalovirus (CMV) promoter-driven luciferase reporter system in KG-1 cells. Moreover, MC3353 displayed strong antiproliferative activity when tested on HCT116 colon cancer cells after 48 h of treatment at 0.5 μM. At higher doses, this compound provided a cytotoxic effect in double DNMT knockout HCT116 cells. MC3353 was also screened on a different panel of cancer cells (KG-1 and U-937 acute myeloid leukemia, RAJI Burkitt's lymphoma, PC-3 prostate cancer, and MDA-MB- 231 breast cancer), where it arrested cell proliferation and reduced viability after 48 h of treatment with IC50 values ranging from 0.3 to 0.9 μM. Compared to healthy cell models, MC3353 induced apoptosis (e.g., U-937 and KG-1 cells) or necrosis (e.g., RAJI cells) at lower concentrations. Importantly, together with the main DNMT3A enzyme inhibition, MC3353 was also able to downregulate the DNMT3A protein level in selected HCT116 and PC-3 cell lines. Additionally, this compound provided impairment of the epithelial-to-mesenchymal transition (EMT) by inducing E-cadherin while reducing matrix metalloproteinase (MMP2) mRNA and protein levels in PC-3 and HCT116 cells. Last, tested on a panel of primary osteosarcoma cell lines, MC3353 markedly inhibited cell growth with low single-digit micromolar IC_{50} ranging from 1.1 to 2.4 μM. Interestingly, in Saos-2 osteosarcoma cells, MC3353 induced both expression of genes and mineralized the matrix as evidence of osteosarcoma to osteoblast differentiation.

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THE INFLUENCE OF Cu(II) IONS ON THE CYSTATIN C STRUCTURE AND FIBRYLLIZATION

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Neurodegenerative diseases constitute one of the major problems of contemporary medicine. The lack of effective drugs and therapy, resulting in the growing number of deaths due to Alzheimer, Parkinson and other dementia diseases, motivates scientists to seek new ideas to solve that issue. To do so, a comprehensive understanding of the mechanism driving protein and peptide aggregation process, which is the basis for these diseases, is necessary.

Previous research carried out on other amyloidogenic proteins, e.g. amyloid β and α-synuclein proved the important role of metal ions in their oligomerization process[1,2]. Copper and zinc, which are found as trace elements essential for proper functioning of the body, probably accelerate brain degeneration. In our project, we have studied the impact of Cu(II) ions on the aggregation and fibryllization of human cystatin C. Incubation of hCC with copper (II) ions caused a significant acceleration of the formation of protein aggregates. The fibryllogenic nature of these ensembles was not confirmed by ThT assay, thereby suggesting their amorphous nature. The most probable copper binding site in the hCC sequence is its C-terminal fragment containing two histidine residues at positions 86 and 90. To confirm our hypothesis, we overproduced in *E. coli* three variants of cystatin C: H90A, H86A and H86A_H90A. Substitution of the histidine residues with non-coordinating alanine significantly influenced the properties of tested proteins and changed their ability to undergo aggregation in the presence of Cu (II) ions.

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NOTES

List of Abstracts

CAMPANICO André	ANTIMYCOBACTERIAL ACTIVITY AND METABOLISM OF (PHOTO)SWITCHABLE N-SUBSTITUTED AZAAURONE E- AND Z-ISOMERIC FORMS	P036
CARLA Varela	STEROIDAL AROMATASE INHIBITORS: C-6ALFA OR C-7ALFA SUBSTITUTION?	P037
CASTRO CARDOSO DE ALMEIDA Helena Carla	NEW AMINO SUGAR-BASED NAPHTHOQUINONES AND ISOQUINOLINE-5,8-DIONES AND THEIR HALOGENATED COMPOUNDS: SYNTHESIS, ANTIBACTERIAL EVALUATION AND IN SILICO ADMET STUDIES	P038
CASTRO CARDOSO DE ALMEIDA Helena Carla	HETERO-DIELS-ALDER REACTIONS OF NOVEL 3-TRIAZOLYL-NITROSOALKENES AS AN APPROACH TO FUNCTIONALIZED 1,2,3-TRIAZOLES WITH ANTIBACTERIAL PROFILE	P039
CASTRO M. Angeles	ANTIPARASITIC HYBRIDS DERIVED FROM QUINOLINE AND TERPENYLNAPHTHOHYDROQUINONES	P040
CAVINA Lorenzo	TOWARDS THE SYNTHESIS OF NOVEL PROTEASE INHIBITORS: LATE-STAGE MODIFICATIONS ALLOWING DIVERGENT SYNTHESIS FROM PEPTIDE-CARBOXYLIC ACIDS	P041
CHAZAPI Evanthia	DESIGN AND SYNTHESIS OF 4-THIATOCOPHEROL/HYDROXYTYROSOL HYBRIDS AS PROTEASOME ACTIVATORS	P042
CHEN Zilin	IN SITU SYNTHESIS OF METAL-ORGANIC FRAMEWORK AND COVALENT ORGANIC FRAMEWORKS MATERIALS ON THE INNER WALL OF CAPILLARIES AS NOVEL STATIONARY PHASES OF CAPILLARY ELECTROCHROMATOGRAPHY FOR PHARMACEUTICAL ANALYSIS	P043
CHENG Ivan	SYNTHESIS AND BIOLOGICAL EVALUATION OF DEPUDECIN ANALOGUES	P044
CHIARAMONTE Niccolo	NEW ENANTIOPURE HYDROXYETHYL-PIPERAZINES AS CARBONIC ANHYDRASE INHIBITORS	P045
CHIONIS Konstantinos	NEW STRATEGIES TO CONTROL TRANSLATION EFFICIENCY BY OLIGONUCLEOTIDES AGENTS	P047
CHO Yong Seo	SYNTHESIS AND BIOLOGICAL EVALUATION OF CHROMANE DERIVATIVES AS S1P1/5 RECEPTOR AGONISTS FOR TREATMENT OF MULTIPLE SCLEROSIS	P048
CHODOUNSKA Hana	NOVEL MOLECULES POTENTIALLY RELIEVING DISORDERS CAUSED BY NMDA RECEPTOR HYPOFUNCTION. STRUCTURE-ACTIVITY RELATIONSHIP	P049
CIESLAK Marcin	THALIDOMIDE-RESEMBLING NEW DICARBOXIMIDES SHOW ANTICANCER AND IMMUNOMODULATORY ACTIVITY VIA TARGETING ABCF1 PROTEIN	P050
CLANTON Nicholas	THE CONCISE, CONVERGENT SYNTHESIS OF SIMPLIFIED TACCALONOLIDES: MICROTUBULE STABILIZERS WITH POTENT ACTIVITY AGAINST TRIPLE NEGATIVE BREAST CANCER	P051
COLLINS Niall	UNDERSTANDING AND EXPLOITING THE ISOMERISATION OF VINYL TO ALLYL SULFONES	P052
CONWAY Lorna	SYNTHESIS OF ANTI-INFLAMMATORY AND PRO-APOPTIC CYCLOPENTENONE PROSTANOID MIMICS	P053
CONWAY Stuart	DESIGN AND SYNTHESIS OF CHEMICAL PROBES FOR BROMODOMAINS	T10
COUPA DESCAMPS Sophie	IDENTIFICATION OF POTENT AND SELECTIVE INHIBITORS OF PHOSPHOINOSITIDE 3-KINASE-BETA (PI3Kb) FOR THE TREATMENT OF PTEN DEFICIENT TUMORS	P054
DA SILVA Gustavo	NOVEL POLYFUNCTIONALIZED INDOLES AGAINST BLOOD STAGE MALARIA PARASITES	P055

IDIRIS Fahima	OPEN SOURCE TUBERCULOSIS (OSTB) SERIES 3: SMALL MOLECULE INHIBITORS OF NON-REPLICATING MYCOBACTERIUM TB	P113
IHNATENKO Irina	BENZAZEPINONE DERIVATIVES AS ANTITRYPANOSOMAL DRUG CANDIDATES	P114
JANSA Petr	SYNTHESIS OF ALKALOID-LIKE COMPOUNDS WITH ALL-CARBON QUATERNARY CENTRES	P115
JEZEQUEL Gwenaëlle	NEW DUAL MOLECULES AS AN INNOVATIVE STRATEGY AGAINST GLIOBLASTOMA: SYNTHESIS AND BIOLOGICAL EVALUATION	P116
JINGYAO LI Jingyao	SYNTHESIS OF HIGHLY SUBSTITUTED 1,3-OXAZINAN-2-ONE DERIVATIVES VIA MULTICOMPONENT REACTION	P117
JOHANSSON Niklas	STRUCTURE OF MEMBRANE BOUND PYROPHOSPHATASE FROM THERMOTOGA MARITIMA IN COMPLEX WITH IMIDODIPHOSPHATE AND N-[(2-AMINOBENZO[d]THIAZOL-6-YL)METHYL] -1H-INDOLE-2-CARBOXAMIDE	P118
JUMPPANEN Mikael	STRUCTURE-ACTIVITY RELATIONSHIP-GUIDED SYNTHESIS AND IN VITRO CHARACTERIZATION OF GATA4 AND NKX2-5 PROTEIN-PROTEIN INTERACTION MODULATORS	P119
JÜNGER Jessica	APPROACH TO THE TOTAL SYNTHESIS OF GULMIRECIN B	P120
KALAMPALIKI Amalia	STUDY OF THE 3-(PYRAZOL-4-yl)INDOLE PHARMACOPHORE FOR THE DEVELOPMENT OF NEW THERAPEUTIC AGENTS FOR CANCER TREATMENT	P121
KAPLANERIS Nikolaos	LATE-STAGE DIVERSIFICATION THROUGH MANGANESE-CATALYZED C−H Activation: ACCESS TO ACYCLIC, HYBRID, AND STAPLED PEPTIDES	P122
KARATAS Mehmet	N-ALKYLATED SULFAMIDES AS NEUTRAL SOLUBILITY IMPROVING GROUPS FOR KINASE INHIBITORS	P123
KARELOU Maria	NOVEL ACRIDINE DERIVATIVES AS TDP 1 AND/OR 2 INHIBITORS	P124
KAWADA Manabu	INTERVENOLIN, A NOVEL ANTI-TUMOR DRUG, SUPPRESSES CANCER CELL GROWTH THROUGH MODULATION OF TUMOR MICROENVIRONMENT	P125
KENG YOON Yeong	DISCOVERY OF A NOVEL NANOMOLAR SELECTIVE BUTYRYLCHOLINESTERASE INHIBITOR	P126
KEUM Gyochang	NOVEL PYRROLO[2,3-d]PYRIMIDINE DERIVATIVES AS TRKA INHIBITOR WITH BROAD SPECTRUM ANTIPROLIFERATIVE ACTIVITY	P127
KHANDAZHINSKAYA Anastasia	ANALOGUES OF 5-SUBSTITUTED PYRIMIDINE NUCLEOSIDES AS ANTIMYCOBACTERIAL AGENTS	P128
KHOMUTOV Alex	METHYLATED SPERMIDINE ANALOGS: SYNTHESIS AND INTERACTION WITH THE ENZYMES OF POLYAMINE METABOLISM	P129
KIM Dae Young	ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF 2,4-DIARYL-1-BENZOPYRANS VIA DECARBOXYLATIVE ALKYLATION OF β-KETO ACIDS TO o-QUINONE METHIDES	P130
KINENA Linda	PEPTIDOMIMETIC PLASMEPSIN INHIBITORS WITH POTENT ANTI-MALARIAL ACTIVITY AND SELECTIVITY AGAINST CATHEPSIN D	P131
KIRKILESSI Olga	DESIGN, SYNTHESIS AND EVALUATION OF MICRONEUROTROPHINS, NOVEL SYNTHETIC AGONISTS OF NEUROTROPHIN RECEPTORS	P132
KLIMCZAK Urszula	HECK REACTION OF CYCLOPROPANATED PYRROLES - SYNTHESIS OF NOVEL NIPECOTIC ACID DERIVATIVES	P133
KLINGLER Franca	EXPLORING THE CHEMICAL SPACE ECONOMICALLY	P134

List of Authors

GŁOGOWSKA	A.	P093, P150
GLYKOFRYDI	P.	P219
GMEINER	P.	P072, P107, P284, P244, P311, P062
GOBEC	S.	P270
GÖBEL	T.	P089
GOBIS	K.	P093, P326, P150
GODOY	F.	P197
GOEBEL	M. W.	P047
GOHLKE	A.	P078
GOIS	P.	P012
GOLAB	J.	P179, P033, P026
GOLAN	A.	P077
GOLDENBERG	S.	P105
GOLDMAN	A.	P118
GOLEBIOWSKI	A.	P179, P033, P026
GOMES	S.	P046
GOMES	A.	P070
GOMES	R.	P253, P094
GÓMEZ	L.	P040
GONÇALVES	P.	P098
GONCALVES AZEVEDO	C.	P017
GONCHARENKO	K.	P095
GONNELLA	N.	T24
GONOS	E. S.	P077
GOODWIN	G.	P078
GOOSSENS	K.	P255
GORE	B.	P307
GOTO	R.	P080
GOTTARDIS	M.	P054
GRABOWSKI	M.	P271
GRAHAM	B.	P324
GRAMMATIKOVA	N.	P213
GRANDANE	A.	P096
GRATAL	P.	P097
GRAVANIS	A.	P156, P203, P132
GRAY	C.	P078
GRAZHDANKIN	E.	P234
GRIERA	M.	P085
GRILO	J.	P098
GRIMM	A.	T24

GRONDAL	E.	T24
GROS	C.	P331
GROSS	G.	P054
GRØTLI	M.	OC04
GROVES	M. .	P316
GRUZA	M. M.	P179
GRZYBOWSKI	M. M.	P026
GUARAGNA	A.	P066
GUDE	L.	P097
GUEDES	R. C.	P012, P056, P086, P237
GUÉRET	S.	OC06
GUERREO	S.	P252
GUILLON	C.	P007
GUL	S.	P237
GUNCHEVA	M.	P013
GUTHY	D. A.	P067
GÜTSCHOW	M.	P160, P306
GUTTORMSEN	Y.	P104
GZELLA	K.	P099
GZIK	A.	P033, P026
HA	Z. Y.	P126
HADDAD	N.	T24
HADJIPAVLOU-LITINA	D.	P219
HADZIMA	M.	P100
HAEGEBARTH	A.	P204
HAGENOW	S.	P278
HAGIHARA	S.	P260
HALLAND	N.	P006
HAMMOCK	B. D.	P162, P108
HAN	J. Y.	P101
HANAYA	K.	P260
HANSEN	E. H.	P104
HANSEN	K.	P104
HARTMAN	A. M.	P102
HASHIMOTO	M.	P080
HASHIMOTO	Y.	P079
HASSAN	G.	P103
HASTINGS	S. D.	P051
HATZIDIMITRIOU	A. G.	P219
HAUG	B. E.	P104
HAUPENTHAL	J.	P141
HAUSMANN	K.	P105

KLAEGER	S.	P180
KLEBL	B.	P104
KLIMCZAK	U.	P133
KLINGLER	F.	P134
KNAPP	S.	P300, P089, P162, P123, P121
KNIPPSCHILD	U.	P168, P184
KNOEPFEL	T.	T26
KOÇ	Î	P294
KOCHETKOV	S. N.	P128
KOEBERLE	A.	OC10
KOEGL	M.	P059
KOHYAMA	A.	P177
KOK	L.	P235
KOKKALI	A.	P220
KOKOTOS	A.C.	P194, P172, P135
KOKOTOS	C.	P287, P304, P206
KOKOTOS	G.	P172, P146, P194, P283, P195, P135, P136
KOKOTOU	M.G.	P146, P194, P136, P287, P304
KOLOCOURIS	A.	P137, P272, P139
KOLSTER PETERSEN	L.	P017
KONC	J.	P270
KONCZAL	J.	P078
KONDO	M.	P211
KONG	Y.	P138
KONSTANTELI	E.	P229
KONSTANTINIDI	A.	P139
KONSTANTINIDOU	M.	P140
KONSTANTINOVIĆ	J.	P141
KONVALINKA	J.	P327
KONZE	K.	OC02
KORA	E.	P145
KORALEWSKI	R.	P179
KORCZ	M.	P020
KORESAWA	E.	P177
KORNICKA	A.	P069, P099
KOROLEV	A.	P213
KORONA-GŁOWNIAK	I.	P326
KÖSE	F. A.	P254
KOSTAKIS	I. K.	P121, P124, P155

KOSTAS	I. D.	P317
KOSTAS	V.	OC03
KOSTOPOULOU	I.	P142
KOSTRHUNOVA	H.	P232
KŐSZEGI	Z.	P062
KOTAŃSKA	M.	P278
KOUFAKI	M.	P231, P077, P042
KOURBELI	V.	P143
KOURGIANTAKI	A.	P132
KOUROUNAKIS	P.	P220
KOUROUNAKIS	A.	P144, P145
KOUSEK	R.	T24
KOUTOULOGENIS	G.	P146
KOUTSOPOULOS	K.	P147
KOWALCZYK	W.	P277
KOWALSKI	M.	P179
KOŽÍŠEK	M.	P327
KOZŁOWSKA	J.	P148
KRALJ	M.	P328
KRAMER	J. S.	P162, P108
KRASNYKH	O.	P149
KRAUSE	M.	P150
KRAUSOVA	B.	P049
KRAUTH-SIEGEL	R. L.	P114
KRAUTLOHER	A.	P231
KRAWCZYK	M.	P109
KRAWIEC	M.	T24
KRCMAR	H.	P181
KRITSI	E.	P132, P231
KRIZ	M.	T24
KRÓLEWSKA-GOLIŃSKA	K.	P050
KRÖNKE	J.	P306
KRÜGER	M.	P168
KRYŠTOF	V.	P187
KUBBUTAT	M.	P173
KUDER	K. J.	P278
KUDOVA	E.	P049, P263
KULBACKA	J.	P205
KUMARI	P.	P151
KUNICK	C.	P199, P123, P114, P073, P257
KURCZAB	R.	P109
KURHADE	S.	P140, P276

LINDHOF	J.	P114
LINDNER	S.	P306
LINDSTEDT	E.-L.	T19
LIPPI	G.	P066
LISTER	A.	P165
LIU	C.	P184
LIU	H.	P110
LOBERTO	N.	P066
LOCARNO	S.	P166
LOCHER	H. H.	T05
LOETSCHER	P.	T26
LOLLI	G.	P321
LOLLI	M.L.	P251
LOPES	E.	P046
LOPES	F.	P036
LOPES	S.	P039
LÓPEZ-ROMERO	J. M.	P230
LORENTZEN	M.	P104
LORENZO	J.	P008
LORENZO	V.	P117
LORICCHIO	E.	P252
LŐRINCZ	E. B.	P018
LOSPINOSO SEVERINI	L.	P252
LOUGIAKIS	N.	P167, P216, P217
LOUREIRO	J.	P046
LOUREIRO	R. S.	P038
LOZAB	M. I.	P289
LUCIA	F.	P245
LUENGO	E.	P183
LUKASHOV	S.	P023
ŁUKOWSKA	W.	P020
LUXENBURGER	A.	P168
LY-BE	C.	P277
LYSENKOVA	L.	P213
MA	S.	P138
MACCHIA	M.	P082, P060
MACEGONIUK	K.	P297
MACHADO	T. R.	P240, P269
MACHARA	A.	P327
MACHESKY	L.	P078
MACIEJEWSKA	N.	P169
MADHAVACHARY	R.	P140
MAES	L.	P111, P112, P029, P255
MAGOULAS	G.	P132
MAGRIOTI	V.	P170
MAGRIOTIS	P.	OC01
MAHUTEAU-BETZER	F.	P202
MAHY	W.	P312
MAI	A.	P331
MAIER	M. E.	P120
MAIORANA	S.	P171
MAIRA	M.	P067
MAJER	P.	P100, P327, P282, P265, P207
MAKRYNITSA	G.	P002
MALI	G.	P139
MALÍNKOVÁ	V.	P187
MANARA	M. C.	P331
MANCHON	L.	P202
MANDRUP BERTOZZI	S.	P028
MANERA	C.	P082, P060
MANSLEY	T.	P076
MANTZOURANI	C.	P172, P135
MARAKOS	P.	P167, P088, P216, P217
MARCANTONI	E.	P247
MARCHINI	M.	P301
MARCOLI	M.	P082
MARES	M.	P100
MARQUES	M. M.	P086, P237, P074
MARTÍNEZ	A.	P208
MARTÍNEZ	J.	P253
MARTÍNEZ-POVEDA	B.	P044
MARTIN-HERNANDO	J. I.	OC08
MARTINI	R.	P237
MARTINS	A. M.	P008
MARUYAMA	K.	P211
MARZARO	G.	P293
MASAOKA	S.	P211
MASCAYANO	C.	P296, P174, P065, P197
MASCAYANO COLLADO	C.	P196
MASI	M.	P273
MASLAH	H.	P261
MASLOVA	V.	P149
MASUDA	T.	P310
MATESANZ	R.	P183

PELINGON	R.	P011
PENNICOTT	L. E.	P258
PENTA	S.	P021
PERDIGÃO	J.	P036
PEREIRA	M.M.	P061
PÉRESSE	T.	P116
PÉREZ	C.	P208
PÉREZ	M.	P040
PERKOVIĆ	I.	P224
PERLMAN	D.	T12
PERTUSATI	F.	P191
PETER VON KRIES	J.	P192
PETRI	M.	P002
PETRIDOU	G.	P142
PETRONCZKI	M.	T24
PETTERSEN	D.	T19
PEYROTTES	S.	P248
PICHLO	C.	P168
PICK	E.	P077
PIIZZI	G.	T12
PILARSKI	B.	P109
PILATTE	I.	P054
PILON	A.	P008
PINTO	T.	P225
PIPPIONE	A.C.	P251
PIRES	A.	P070
PISSOT-SOLDERMANN	C.	OC05
PITSA	I.	OC01
PITTEROU	I.	P142
PLAKANTONAKI	M.	P139
PLETTENBURG	O.	T03
PŁOSKOŃSKA	A.	P020
PLUT	E.	P226
PLUTA	E.	P179
POGORYELOV	D.	P162, P108
POKORNÁ	J.	P327
POLI	G.	P242
POLINI	B.	P082, P060
POLITI	E.	P227
POLITIS	P. K.	P172, P135, P194
POLLINGER	J.	P228
POMMIER	Y.	P121, P124
PONCELET	V.	P054

PONIMASKIN	E.	P109
PONTILLO	A. R. N.	P229
POPENKO	V. I.	P128
POPIK	P.	P109
POPIOŁEK-BARCZYK	K.	P109
PORATTI	M.	P293
PORRAS-ALCALÁ	C.	P230
PORTEL	J. F.	P008
PORTUGAL	I.	P036
POTANIEC	B.	P148
POULI	N.	P167, P186, P088, P216, P217
POURNARA	D.	P231
POWELL	J.	P265
PRACHAROVA	J.	P232
PRATSCH	D. G.	P072
PRECHTL	S.	P204
PREU	L.	P123, P114
PREVITALI	V.	P233
PREVITI	S.	P171
PRINZ	F.	P204
PROENÇA	C.	P267
PROKOFEVA	P.	P180
PROSCHAK	E.	P162, P108, P089
PROTOPOPOV	M.	P023
PROUSIS	K.	P077, P203, P132, P042, P156
PROVENZANI	R.	P234
PRUDÊNCIO	M.	P098
PRUGAR	L. I.	P300
PSARRA	A.	P283
PSOMAS	G. .	P218
PU	S.-Y.	P300
PUDNIKA	L.	P096
PUGLIESE	A.	P078
PURWANTINI	I.	OC07
PUSHECHNIKOV	A.	P153
PUTHA	L.	P235
QUANCARD	J.	OC05
QUEROLLE	O.	P054
QUESADA	A. R.	P044
QUEST	A. F. G.	P252
QUINN	R. J.	P193

QUIROZ	J.	P197
RADETZKI	S.	P192
RAIMUNDO	L.	P046
RAIS	R.	P282, P265, P207
RAITANEN	J.-E.	P064
RAJIĆ	Z.	P224
RAMILO-GOMES	F.	P237
RAMJI	K.	P026
RAMOS LLORCA	A.	P238
RANIOLO	S.	P185
RANK	J.	P181
RANUCCI	S.	P066
RASCAL	E.	P261
RASSIAS	G.	P241, P295
RAVASCO	J. M. J. M.	P242
RECIO	J.	P243
REEVES	J.	T24
REINECKE	M.	P180, P181
REIS	F.	P046
REISER	O.	P133, P226
REKKA	E.	P220
RENATUS	M.	OC05
RENAUD	P.	P281, P010
RENGARASU	R.	P120
RESSURREIÇÃO	A. S.	P098
REUILLON	T. D.	P258
REYNOSO-MORENO	I.	P082
ŘEZÁČOVÁ	P.	P327
REZEKIN	I.	P152
ŘEZNÍČKOVÁ	E.	P187
RIBAUDO	G. [.	P321
RIBEIRO	D.	P267
RICCIO	A.	P053
RICKLIN	D.	P024
RISEL	P.	P244
RISINGER	A. L.	P051
RITMALENI	R.	OC07
RITZ	D.	T05
ROBAA	D.	P105
ROBBASON	B.	OC02
ROBERT	X.	P007
ROBERTA	F.	P245

ROBERTS	L.	T12
ROBERTSON	M.	P025
ROBLES	T. R.	T12
ROCA	C.	P208
ROCCHIO	I.	P301
ROCCO	L.	P066
ROCHAIS	C.	P288
RODRIGUES	CAT.	P253
RODRIGUES	CE. M. P.	P074
RODRIGUES	L.	P012
RODRIGUES	CAR.	P239, P240, P268, P269
RODRIGUES-JUNIOR	V.	P224
RODRIGUEZ-CALADO	S.	P008
RODRÍGUEZ-PUYOL	D.	P085
RODRÍGUEZ-PUYOL	M.	P085
RODZIEWICZ-MOTOWIDŁO	S.	P081
ROECKLIN	D.	P173
ROGDAKIS	A.	P203
ROGGE	T.	P122
ROHRBACH	S.	P281
ROJAS	C.	P265
ROJÍKOVÁ	K.	P327
ROLEIRA	F.	P037, P070, P267
ROMANELLI	G.	P253
ROMANELLI	M. N.	P045
ROMIER	C.	P105
ROSENBAUM	D.	P107
ROSSETTI	A.	P246
ROSSI	A.	P066
ROSSI	F. V.	P247
ROTA	F.	P031
ROTH	B.	P109
RŐTH	E.	P018
ROUMANA	A.	P002
ROUSSI	F.	P116
ROUSSIS	V.	P091
ROUTIER	S.	P320
ROUX	B.	P054
ROVATI	G. E.	P162
ROY	M. J.	P059
ROY	O.	P280
ROY	B.	P248

SCHUBERT-ZSILAVECZ	M.	P089
SCHÜTTELKOPF	A.	P078
SCHWARDT	O.	P024
SCHWEDA	S.	P257
SCOTLANDI	K.	P331
SCOTT	F.	P258
SEGALL	M.	P076
SEHR	P.	P198
ŞENOL DENIZ	F. S.	P016
SEO	E.-J.	P227
SEROCKI	M.	P212, P169
SERPI	M.	P191
SERRA	S.	P261
SHAABANI	S.	P316, P084
SHAIK	T. S.	P105
SHARPS	B.	T24
SHAV-TAL	Y.	P001
SHCHEKOTIKHIN	A.	P213, P034, P285
SHEN	A.	P110
SHIBASAKI	M.	P310, P125
SHINDO	N.	P259
SHOJI	M.	P260
SIAMIDI	A.	P221
SIEGEL	F.	P204
SIIROLA	E.	OC11
SILVA	A.M.S.	P055
SILVA	E. R.	P008
SILVA	F.	P039
SILVA	W. A.	P038
SIMEONOV	S.	P253
SIMIC	O.	OC05
SIMONE	G.	P245
SIMOV	B. P.	T24
SINGH	D. K.	P157
SINGH	K.	P313
SIOPA	F.	P242
SIOZOS	V.	P090
SIPARI	N.	P103
SIPPL	W.	P105
SIPTHORP	J.	P312
SIRVINSKAITE	G.	P122
SIWIEC	M.	P109
SIWINSKA	A. M.	P026

SIZOVA	S.	P004
SKARBEK	C.	P261
SKIBISZEWSKA	S.	P262
SKLADANOWSKI	A.	P106
SKLEPKIEWICZ	P.	P179
SKOBRIDIS	K.	P303, P209
SKOWRON	P.	P332
SLAVIKOVA	B.	P049, P263
SLUSHER	B. S.	P282, P265, P207
SMIRNOVA	T. G.	P128
SMITS	R.	P264
ŠNAJDR	I.	P265
SNAJDROVA	R.	OC11
SOBRAL	L.	P237
SOFIADIS	M.	T22
SOLCA	F.	T24
SOLODNIKOV	S.	P149
SONG	Y.	P266
SORGE	M.	OC05
SOROKIN	D.	P034
SORRELL	F. J.	P300
SOSNOWSKA	A.	P026
SOUSA	S. A.	P008
SOUZA	M. C. B. V.	P038
SOUZA	A.	P268, P269, P240
SOVA	M.	P270
SPANKA	C.	OC05
SPYROULIAS	G. A.	P002
SRIBAR	D.	P271
SRISHYLAM	P.	P021
STADTMÜLLER	H.	T24
STAMATIS	D.	P137, P272
STAMPOLAKI	M.	P272
STANCZAK	P. S.	P033, P026
STARHA	P.	P232
STARK	H.	P278
STARR	J. T.	P247
STASEVYCH	M.	P212, P169
STAUFFER	F.	P067
STAZI	G.	P331
STEADMAN	D.	P312
STEFEK	M.	P147

ZAK	A.	P320
ZALUBOVSKIS	R.	P096
ZAMBOULI	A.	P135
ZAMPERINI	C.	P245
ZANCHIN	N. T.	P105
ZANFORLIN	E.	P321
ZANGIROLAMI	A.	P061
ZANTZA	I.	P185
ZAPPALÀ	M.	P171
ZÁRATE	A. M.	P252
ZECHA	J.	P181
ZEMKOVA	H.	P263
ZERVOU	M.	P132
ZETSCHOK	D.	P322
ZHANG	B.	P323
ZHAO	Y.	P312
ZHOU	J.	P315
ZHOU	H.	P325
ZIEMBICKA	D.	P093, P326
ZIMA	V.	P327
ZIMMERMANN	R.	P103
ZLATIĆ	K.	P328
ZOEPHEL	A.	T24
ZOGALI	V.	P295, P241
ZOGOTA	R.	P131
ZOIDIS	G.	P222, P090, P329
ZOLLMAN	D.	P059
ZONTA	F.	P321
ZORE	M.	P330
ZOUMPOULAKIS	P.	P231
ZUBRIENĖ	A.	P063
ŽUKAUSKAITĖ	A.	P187
ZUMBRUNN	C.	T05
ZVARYCH	V.	P212, P169
ZWERGEL	C.	P331
ZYGOWSKA	J.	P332

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