**Emerging therapies for acute myeloid leukaemia using hDHODH inhibitors**

# EFMC | ACSMEDI
# Medicinal Chemistry Frontiers 2019

## Krakow, Poland | June 10-13, 2019

# BOOK OF ABSTRACTS

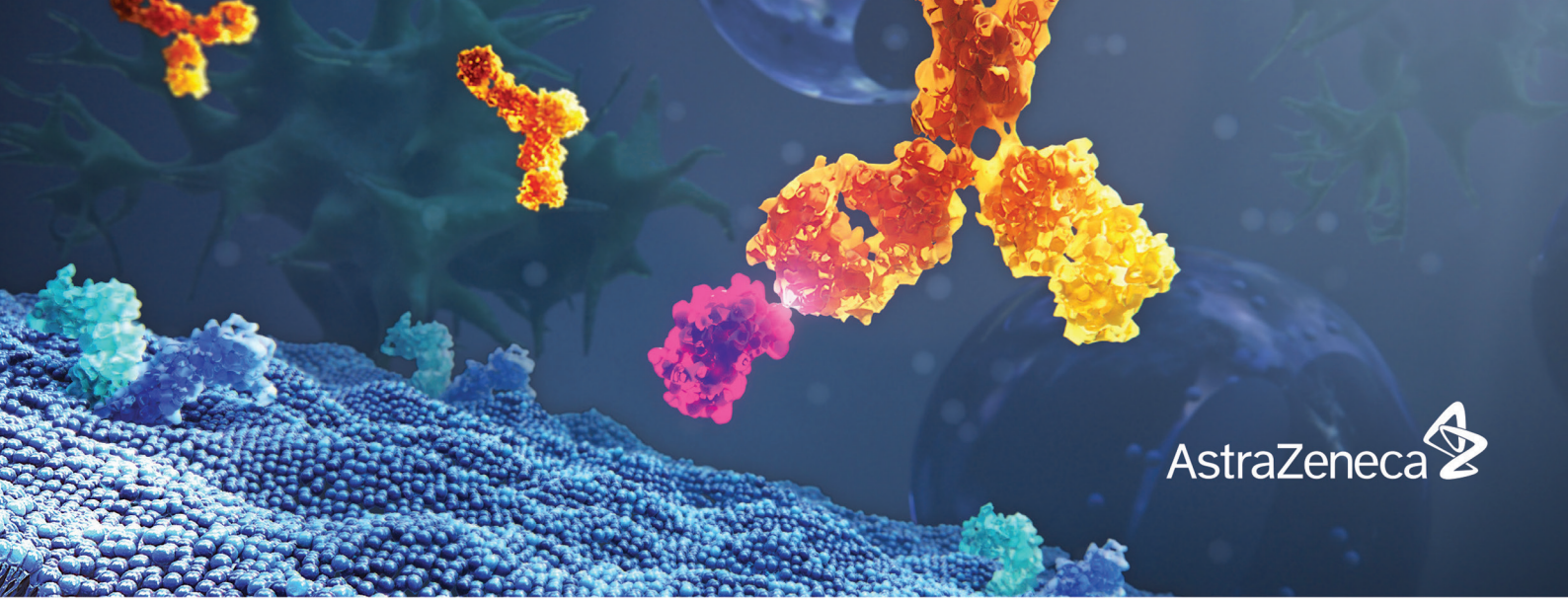
Jointly organised by

EFMC
European Federation
for Medicinal Chemistry

ACS Technical Division
Medicinal Chemistry (MEDI)

POLISH SOCIETY
OF MEDICINAL CHEMISTRY

www.medchemfrontiers.org

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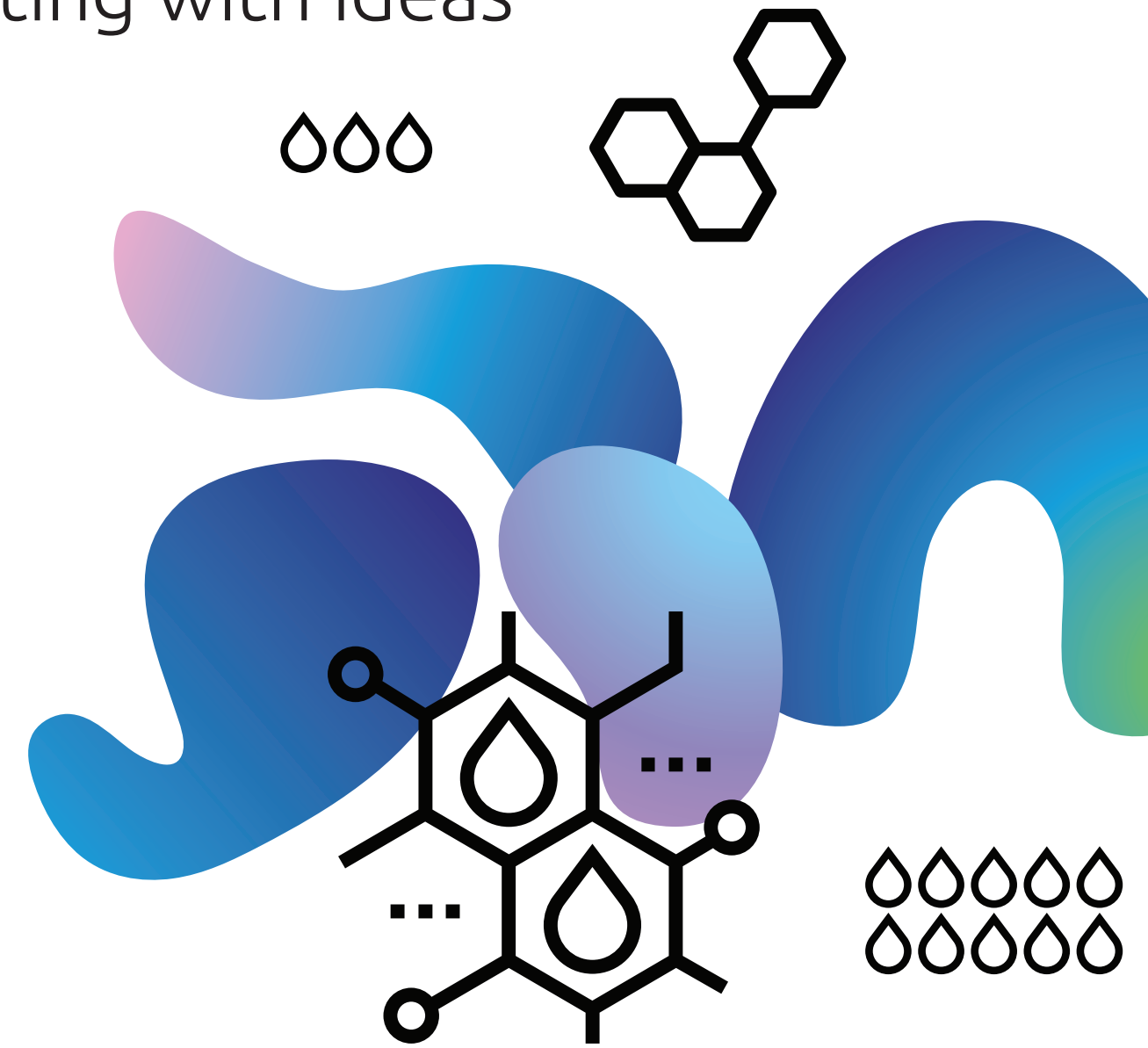

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# Welcome

Dear Participant,

On behalf of the International Organising Committee, it is our pleasure to welcome you to the EFMC-ACSMEDI MedChem Frontiers 2019 in Krakow, Poland. The meeting is jointly organised by the European Federation for Medicinal Chemistry (EFMC) and the Division of Medicinal Chemistry of the American Chemical Society (ACSMEDI). This symposium is the seventh in a series initiated in 2007 in Siena, Italy, and since then taking place alternatively in Europe and in the USA. The local organiser for this edition is the Polish Society of Medicinal Chemistry.

We are very pleased that MedChem Frontiers 2019 attracted about 300 scientists from all over the world, and we hope this will offer ample opportunities for networking with colleagues from medicinal chemistry, chemical biology and other areas of drug discovery. We aim to highlight the latest advances in medicinal chemistry during the symposium, with plenary lectures and themed sessions on a diversity of scientific topics. These will be complemented with selected oral communications, and about 120 posters.

The city of Krakow has many things to offer. It is Poland's second largest city and the country's main tourist destination. The city remains the cultural capital of Poland. With seven universities and nearly twenty other institutions of higher learning, Krakow is the country's principal center of science and education. The city boasts hundreds of historical buildings, from medieval churches to Art Nouveau edifices, as well as famous musea. Krakow is also is famed in Poland for its energetic nightlife.

We will do our best to ensure that you have a good experience at the EFMC-ACSMEDI MedChem Frontiers 2019, and wish you a scientifically rewarding and enjoyable stay in Krakow.

Dr Yves P. Auberson
*EFMC President*
*Novartis, Switzerland*

Prof. Katarzyna Kiec-Kononowicz
*Symposium Chair*
*Jagiellonian University, Poland*

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# Programme

## MONDAY JUNE 10, 2019

**10:00** Optional Excursions

**15:00** Registration

**17:30** Opening of the Symposium & Welcome Address

**17:45** ***Derivatives of 1,3,5-triazine as a New Trend in the Search for the 5-HT$_6$ Receptor Ligands with Therapeutic Perspectives*** **(PL01)**
Dr Jadwiga HANDZLIK *(MEDICAL COLLEGE OF JAGIELLONIAN UNIVERSITY, Krakow, Poland)*

**18:30** Welcome Reception

## TUESDAY JUNE 11, 2019

**08:00** Registration

**Matrix Metallo-Proteinases**

**Session Chair :** Prof. Krzysztof JOZWIAK *(MEDICAL UNIVERSITY OF LUBLIN, Lublin, Poland)*

**09:00** ***Libraries of Fluorogenic Substrates with Natural and Unnatural Amino Acids as a Tool in Design of Active and Specific Probes for Investigation of Proteolytic Enzymes*** **(IL01)**
Prof. Marcin DRAG *(WROCLAV UNIVERSITY OF TECHNOLOGY, Wroclaw, Poland)*

**09:30** ***MMP-9 at the Synapse in the Brain and Mind*** **(IL02)**
Prof. Leszek KACZMAREK *(NENCKI INSTITUTE OF EXPERIMENTAL BIOLOGY, Warsaw, Poland)*

**10:00** ***Metalloproteinase Cleavage Control of Interferon Alpha and Gamma Dampens Inflammation and Anti-Viral Immunity*** **(IL03)**
Prof. Christopher OVERALL *(UNIVERSITY OF BRITISH COLUMBIA, Vancouver, Canada)*

**10:30** Coffee Break and Exhibition

**Genomics in Drug Discovery : Roles for Chemistry**

**Session Chair :** Prof. Terry MOORE *(UNIVERSITY OF ILLINOIS, Chicago, United States)*

**11:00** ***Designing Synthetic Gene Regulators (SynGRs)*** **(IL04)**
Prof. Aseem ANSARI *(UNIVERSITY OF WISCONSIN-MADISON, Madison, United States)*

**11:30** ***Exploring Bacterial Genomes for Natural Product Discovery and Development*** **(IL05)**
Prof. Alessandra S. EUSTAQUIO *(UNIVERSITY OF ILLINOIS AT CHICAGO, Chicago, United States)*

**12:00** ***Integrative Screening Identifies a Novel Node in the Oncogenic YAP/HIPPO Pathway*** **(IL06)**
Dr Mathias FREDERIKSEN *(NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH (NIBR), Basel, Switzerland)*

**12:30** Lunch and Exhibition

**Advances in Protein Degradation Technologies**

**Session Chair :** Prof. Daniel HARKI *(UNIVERSITY OF MINNESOTA, Minneapolis, United States)*

**14:00** ***Targeted Protein Degradation with Small Molecules: how PROTACs Work*** **(IL07)**
Prof. Alessio CIULLI *(UNIVERSITY OF DUNDEE, Dundee, United Kingdom)*

**14:30** ***The Ubiquitin System*** **(IL08)**
Prof. Huib OVAA *(LEIDEN UNIVERSITY MEDICAL CENTER, Leiden, The Netherlands)*

**15:00** ***Small-Molecule Modulation of Cereblon Protein Level*** **(OC01)**
Mr Christian STEINEBACH *(UNIVERSITY OF BONN, Bonn, Germany)*

**15:15** ***Drugging Challenging E3 Ligases: A Novel Multidisciplinary Approach to Identify Small-Molecules that Bind FBW7*** **(OC02)**
Ms Míriam MARTÍNEZ-CARTRÓ *(UNIVERSITY OF BARCELONA, Barcelona, Spain)*

**15:30** Coffee Break and Exhibition

**Session Chair :** Prof. Andrzej BOJARSKI *(INSTITUTE OF PHARMACOLOGY POLISH ACADEMY OF SCIENCES, Krakow, Poland)*

**16:00** ***Systems Pharmacology Links GPCRs with Retinal Degenerative Disorders*** **(PL02)**
Prof. Krzysztof PALCZEWSKI *(CASE WESTERN RESERVE UNIVERSITY, Cleveland, United States)*

**16:45** ***First Time Disclosure***
***The Discovery of LML134, a Histamine H3 Receptor Inverse Agonist for the Clinical Treatment of Excessive Sleep Disorders*** **(IL09)**
Dr Yves P. AUBERSON *(NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, Basel, Switzerland)*

**17:15** **Poster Session 1** (Posters with odd numbers)

**18:15** City Tour

## WEDNESDAY JUNE 12, 2019

### GPCRs: a Discovery Powerhouse

**Session Chair :** Dr Yves P. AUBERSON *(NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, Basel, Switzerland)*

**09:00** ***G Protein-Coupled Receptors: the Structural Basis for their Pharmacology*** **(IL10)**
Dr Chris TATE *(MRC LABORATORY OF MOLECULAR BIOLOGY, Cambridge, United Kingdom)*

**09:30** ***Design of Orexin-1 Receptor Selective Antagonists*** **(IL11)**
Dr Uta LESSEL *(BOEHRINGER INGELHEIM, Biberach an der Riss, Germany)*

**10:00** ***Next Generation GPR119 Agonists as Potential Treatment for Cardiometabolic Diseases*** **(IL12)**
Dr Lothar SCHWINK *(SANOFI, Frankfurt Am Main, Germany)*

**10:30** Coffee Break and Exhibition

### Specific and Multi-Targeted Drugs

**Session Chair :** Prof. Andrzej BOJARSKI *(INSTITUTE OF PHARMACOLOGY POLISH ACADEMY OF SCIENCES, Krakow, Poland)*

**11:00** ***Charting New Paths in Multi-Target Drug Discovery for Alzheimer's Disease*** **(IL13)**
Prof. Maria Laura BOLOGNESI *(UNIVERSITY OF BOLOGNA, Bologna, Italy)*

**11:30** ***Multiple Targeting - The Histamine H3 Receptor Pharmacophore as Central Element*** **(IL14)**
Prof. Holger STARK *(HEINRICH HEINE UNIVERSITY DÜSSELDORF, Duesseldorf, Germany)*

**12:00** ***Chemical Biology for Drug Discovery: A Click and Play Approach Exemplified by ERK1/2 Probes*** **(OC03)**
Dr Charlotte GRIFFITHS-JONES *(ASTEX PHARMACEUTICALS, Cambridge, United Kingdom)*

**12:15** ***Identification and in-vivo Efficacy Studies of a Nicotinamide Derivative as Novel NNMT Inhibitor*** **(OC04)**
Dr Sven RUF *(SANOFI-AVENTIS DEUTSCHLAND GMBH, Frankfurt am Main, Germany)*

**12:30** Lunch and Exhibition

### Opioid, Pain, Endo-Cannabinoid

**Session Chair :** Prof. Katarzyna KIEC-KONONOWICZ *(JAGIELLONIAN UNIVERSITY, Krakow, Poland)*

**14:00** ***Cannabinoid Receptor Type 2 Modulation to Improve Outcomes for Cartilage Repair in the Osteoarthritic Joint*** **(IL15)**
Prof. Katarzyna STAROWICZ-BUBAK *(INSTITUTE OF PHARMACOLOGY, POLISH ACADEMY OF SCIENCES, Krakow, Poland)*

**14:30** ***Potential of Natural Cannabinoids and Synthetic Cannabinoids in Neuroprotection*** **(IL16)**
Prof. Rafael FRANCO *(UNIVERSITY OF BARCELONA, Barcelona, Spain)*

**15:00** ***Discovery of Best in-class, Novel, Selective, Potent and Peripheral FLT3 Inhibitors, a New Way to Treat Neuropathic Pain*** **(OC05)**
Dr Dominique SURLERAUX *(BCI PHARMA, Liège, Belgium)*

**15:15** ***The Discovery and Development of the Clinical FAAH Inhibitor JNJ-42165279*** **(OC06)**
Prof. James BREITENBUCHER *(UNIVERSITY OF CALIFORNIA SAN FRANCISCO, San Francisco, United States)*

**15:30** Coffee Break and Exhibition

**Session Chair :** Prof. Terry MOORE *(UNIVERSITY OF ILLINOIS, Chicago, United States)*

**16:00** ***Next Generation Pain Therapeutics for the Opioid Crisis: Design of Bifunctional Nociceptin/Mu Opioid GPCR Ligands as non-Addicting Analgesics*** **(PL03)**
Dr Nurulain ZAVERI *(ASTRAEA THERAPEUTICS, Mountain View, United States)*

### Pharma Research Highlights in Poland

**16:45** ***Discovery of OAT-2068 - A Potent, Selective, Orally Bioavailable Inhibitor of Mouse Chitotriosidase and its In Vivo Activity in the Bleomycin-Induced Pulmonary Fibrosis Model in Mice*** **(OC07)**
Dr Agnieszka BARTOSZEWICZ *(ONCOARENDI THERAPEUTICS SA, Warszawa, Poland)*

**17:00** ***DPD-inspired Small Heterocyclic Libraries Characterized as Novel LsrK Kinase Inhibitors: an Opportunity to Fight Antimicrobial Resistance*** **(OC08)**
Dr Anna KARAWAJCZYK *(SELVITA, Krakow, Poland)*

**17:15** **Poster Session 2** (Posters with even numbers)

**18:15** End of Poster Session

**20:00** Symposium Banquet

| THURSDAY JUNE 13, 2019 | |
|---|---|
| **Chemical Biology Tools & Target Engagement Technologies** | |
| **Session Chair :** Prof. Edgars SUNA *(LATVIAN INSTITUTE OF ORGANIC SYNTHESIS, Riga, Latvia)* | |
| 09:00 | ***Protein-Ligand Interactions: How Medicinal Chemistry Contributes to the Understanding of Molecular Recognition*** **(IL17)**<br>Dr Marc NAZARE *(FMP, Berlin, Germany)* |
| 09:30 | ***Adventures in Targeting Protein Lipdation: Breaking Drug Resistance Using Fragment Deconstruction and Chemical Biology*** **(IL18)**<br>Prof. Edward TATE *(IMPERIAL COLLEGE LONDON, London, United Kingdom)* |
| 10:00 | ***Chemical Physiology of Antibody Conjugates and Natural Products*** **(IL19)**<br>**«2018 MedChemComm Emerging Investigator Lectureship»**<br>Dr Goncalo BERNARDES *(INSTITUTO DE MEDICINA MOLECULAR, Portugal & UNIVERSITY OF CAMBRIDGE, Cambridge, United Kingdom)* |
| 10:30 | Coffee Break and Exhibition |
| **Targeted Covalent Inhibitors** | |
| **Session Chair :** Dr. Anders KARLÉN *(UPPSALA UNIVERSITY, Uppsala, Sweden)* | |
| 11:00 | ***Safety First: Covalent Inhibitors from a Safety Perspective*** **(IL20)**<br>Dr Mickael MOGEMARK *(ASTRAZENECA, Mölndal, Sweden)* |
| 11:30 | ***Adventures in Functional Assignment and Inhibition of Metallo-Enzymes*** **(IL21)**<br>Prof. Christopher J. SCHOFIELD *(UNIVERSITY OF OXFORD, Oxford, United Kingdom)* |
| 12:00 | ***Mining the Protein Kinase Cysteinome*** **(IL22)**<br>Dr Tjeerd BARF *(ACERTA PHARMA BV, Oss, The Netherlands)* |
| 12:30 | Lunch and Exhibition |
| **Adding AI to the Drug Discovery Tool Box** | |
| **Session Chair :** Dr Carolyn DZIERBA *(BRISTOL-MYERS SQUIBB, Wallingford, United States)* | |
| 14:00 | ***Learning the Art of Chemical Synthesis with Deep Neural Networks and Discipline Scale Data*** **(IL23)**<br>Prof. Mark WALLER *(UNIVERSITY OF WOLLONGONG, Wollongong, Australia)* |
| 14:30 | ***Applications of Artificial Intelligence in Drug Discovery – Separating Hype From Utility*** **(IL24)**<br>Dr Pat WALTERS *(RELAY THERAPEUTICS, Cambridge, United States)* |
| 15:00 | ***Augmented Intelligence for Compound Design*** **(OC09)**<br>Dr Michal WARCHOL *(ARDIGEN, Krakow, Poland)* |
| 15:15 | ***Capturing and Applying Knowledge to Guide Compound Optimisation*** **(OC10)**<br>Dr Nick FOSTER *(OPTIBRIUM, Cambridge, United Kingdom)* |
| 15:30 | Closing Remarks |

# Social Programme

Maximise your networking opportunities by taking part in the social activities! The Social Programme of the Symposium will include:

## Welcome Reception on Monday, June 10

Participation in the Welcome Reception is free of charge for all registered participants. The Welcome Reception will take place in the Exhibition area, from 18:30 to 19:30.

## City Tour on Tuesday, June 11

At the end of the scientific programme on Tuesday, a city tour is organised from 18:15 until 19:30 to give participants the chance to discover Krakow.

You will enjoy a stroll around in the Main Market and the Wawel Castel.

This activity is free of charge, but subject to prior booking.

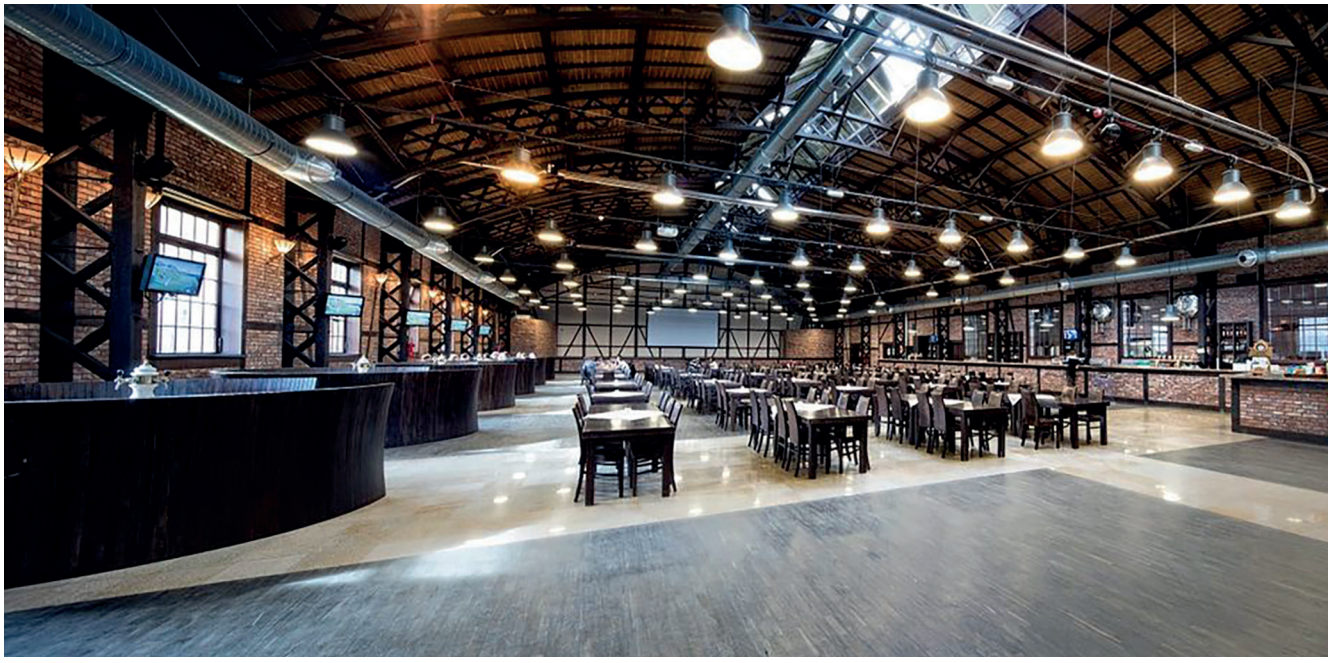
## Symposium Banquet on Wednesday, June 12

The Symposium Banquet will take place at the Zajezdnia tram depot, starting at 20:00.

Participation in the Banquet is optional, and subject to prior booking at the price of € 65,00. If you have booked the Banquet during your registration process, you will have a ticket in your delegate envelope.

Please take this ticket with you in order to get access to the restaurant.

For last-minute reservations please pass at our desk.



# General Information

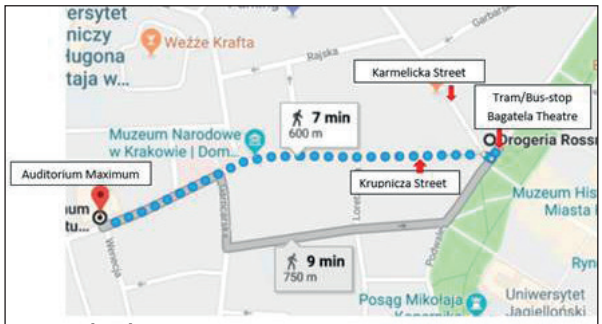
## Venue

EFMC-ACSMEDI Medicinal Chemistry Frontiers 2019 is taking place at:

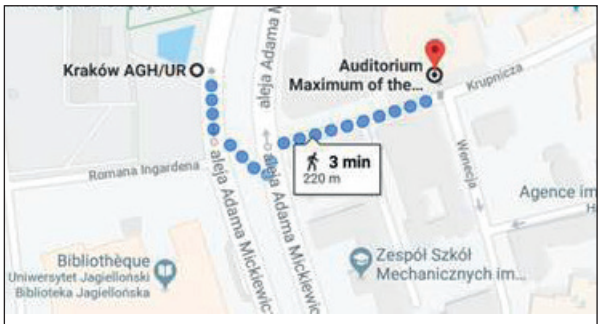
**Jagiellonian University**
Auditorium Maximum
Krupnicza 33
31-123 Krakow
Poland

## How to Get There?

The two closest tram/bus stops to reach Auditorium Maximum are 'Bagatela Theatre' and 'AGH / UR'.




**Bargatela Theatre**
*(7 minutes walking distance from the East side of the city)*




**AGH / UR**
*(3 minutes walking distance from the West side of the city)*

## Registration Package

The registration package for conference participants includes:

- Welcome reception on Monday evening
- Admission to all scientific sessions and to the exhibition programme
- Abstract book, symposium bag and certificate of attendance
- Lunches and refreshment breaks as per the symposium schedule
- The possibility to book additional activities included in the Social Programme

## Registration Desk

The Registration Desk will be open during the following hours:

- Monday, June 10 from 15:00-19:30
- Tuesday, June 11 from 08:00-18:15
- Wednesday, June 12 from 08:00-18:15
- Thursday, June 13 from 08:00-15:30

## Name Badge

All participants are requested to wear their name badges during the symposium and the social events. The name of the participant, affiliation, city and country of origin will appear on the badge.

## Poster Sessions

Mounting stickers will be provided in your welcome envelope. Posters can be displayed during the whole duration of the conference.

Poster presentations will take place in two sessions:

- Tuesday, June 11 from 17:15 to 18:15 (odd numbers)
- Wednesday, June 12 from 17:15 to 18:15 (even numbers)

Posters should be dismounted at the very latest during the lunch break on Thursday. All remaining posters will be removed and disposed of by the conference secretariat.

## Internet Connection

WiFi internet connection will be available for all conference participants.

- network: UJ_Wifi
- Login: maximumwifi@uj.edu.pl
- password: #MCFrontiers19

## Coffee Breaks & Lunches

Coffee breaks and buffet lunches are included in the registration package and will be served in the exhibition area at the time mentioned in the programme schedule.

## Special Diet Requirements

If you have specified special dietary requirements during your online registration, a coloured badge will be included in your delegate envelope. Please show this badge to one of the waiters during the lunch breaks and you will be served a special tray in accordance with your requirements. The same applies if you have booked a ticket for the symposium banquet.

## Official Language

The official language of the symposium is English. No simultaneous translation will be provided.

## Certificate of Attendance & Poster Presentation

A certificate of attendance and poster presentation (if applicable) will be provided to all participants in the registration package. Participants requiring an original stamp and signature should present their certificate at the Registration desk.

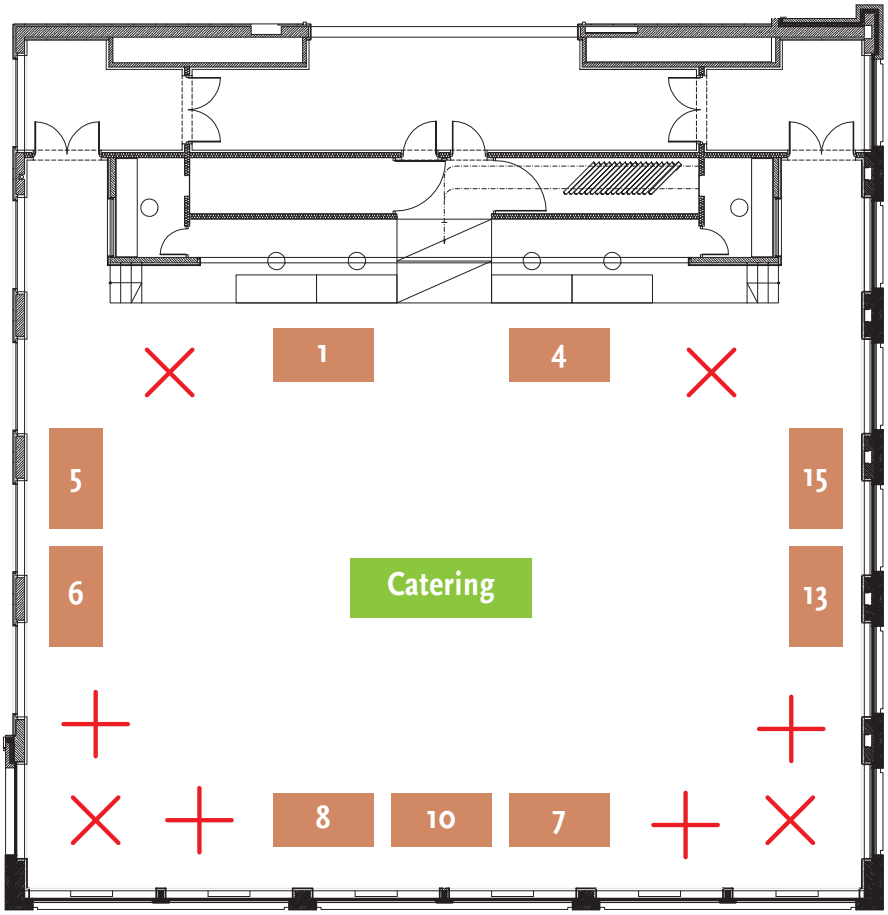
## Liability & Insurance

Neither the Organisers nor LD Organisation will assume any responsibility whatsoever for damage and injury to persons or property during the Symposium. Participants are recommended to arrange for their personal travel and health insurance.

## Emergencies

For any urgent question during the conference, you can reach us on our mobile phone: **+32 472 65 14 60**.

## Floorplan




## Exhibitors

| | |
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# ALWAYS CURIOUS

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**Andrey Tarnovskiy**
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**Danielle Bradshaw**
danielleb@fluorochem.co.uk | www.fluorochem.co.uk | www.dougdiscovery.com

## Iktos

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**Adam Skiredj**
adam.skiredj@iktos.com
www.iktos.ai

## Manchester Organics

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**Patrycja Roszkowska**
info@manchesterorganics.com | www.manchesterorganics.com

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info@mercachemsyncom.com | www.mercachemsyncom.com

## Optibrium Ltd.

Optibrium provides software for drug design, optimisation and data analysis. It's lead product, StarDrop, is a comprehensive suite of integrated software with a highly visual and user-friendly interface. StarDrop enables a seamless flow from the latest data through to predictive modelling and decision-making regarding the next round of synthesis and research, improving the speed, efficiency, and productivity of discovery.

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**Nick Foster**
info@optibrium.com | www.optibrium.com

## PerkinElmer

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kamila.olejnik@perkinelmer.com | www.perkinelmer.com

## Selvita S.A.

Selvita S.A. is a clinical stage drug discovery company engaged in the research and development of novel cancer therapies, as well as provision of integrated drug discovery services. Selvita is headquartered in Krakow with offices in the U.S. and U.K. The company is listed on the Warsaw Stock Exchange (WSE:SLV).

Bobrzynskiego 14 | 30-348 Krakow | Poland

**Malgorzata Syjud**
malgorzata.syjud@selvita.com | www.selvita.com

**Novartis Institutes for BioMedical Research**
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At Novartis, we harness the innovation power of chemical biology and medicinal chemistry to address some of society's most challenging healthcare issues. Our researchers work to push the boundaries of science, broaden our understanding of diseases and develop novel products in areas of great unmet medical need. We are passionate about discovering new ways to extend and improve patients' lives.

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## NOTES

# PLENARY & INVITED LECTURES – ABSTRACTS & BIOSKETCHES

# Dr Jadwiga HANDZLIK

MEDICAL COLLEGE OF JAGIELLONIAN UNIVERSITY, KRAKOW, POLAND

Jadwiga Handzlik is Associate Professor of Medicinal Chemistry in the Department of Technology and Biotechnology of Drugs, Jagiellonian University, Medical College in Cracow. She completed her Ph.D. in medicinal chemistry at the Faculty of Pharmacy, JU MC in Cracow in the group of. Prof. Katarzyna Kieć-Kononowicz (2006). In 2013, she received Doctor of Sciences Degree in pharmacy (habilitation) for work on pharmacophore features responsible for discrimination between GPCRs and MDR-protein targets. She is co-founder (2007) and activist of Polish Medicinal Chemistry Society, Participant of several COST actions and Co-organizer of Drug Discovery and Development course for international students at the Faculty of Pharmacy JU MC (2018). Her scientific expertise concerns computer-aided design and synthesis of GPCRs ligands and MDR modulators, including experience in screening *in vitro* and *in vivo*. Recently, her main interest is focused on serotonin receptors 5-$HT_6$.

# DERIVATIVES OF 1,3,5-TRIAZINE AS A NEW TREND IN THE SEARCH FOR THE 5-HT6 RECEPTOR LIGANDS WITH THERAPEUTIC PERSPECTIVES

**Jadwiga Handzlik (1), Rafał Kurczab (2), Dorota Łażewska (1), Małgorzata Więcek (1), Magdalena Jastrzębska-Więsek (1), Grzegorz Satała (2), Wesam Ali (1,3), Monika Głuch-Lutwin (1), Barbara Mordyl (1), Magdalena Kotańska (1), Annamaria Lubelska (1), Gniewomir Latacz (1), Agata Siwek (1), Anna Partyka (1), Anna Wesołowska (1), Claus Jacob (3), Katarzyna Kieć-Kononowicz (1)**

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Among the GPCR serotonin receptors, the 5-$HT_6$ subtype is a most recently identified (1993) and the most diverse from the rest due its structure, localization and functions [1]. Only 5-$HT_6$Rs are almost exclusively located in CNS. Especially important is the localization of 5-$HT_6$R in the prefrontal cortex (PFC), which is critical to normal cognitive processes, including: attention, impulsivity, planning, decision-making, working memory, and learning or recall of learned memories [2]. Thus, 5-$HT_6$R ligands can be considered as pivotal for innovative treatment of cognitive impairment, with special accent on the 5-$HT_6$R antagonists, although both agonists and antagonists have been found as profitable to improve cortical performance in different paradigms assessing cognitive flexibility and learning and memory or to reverse deficits induced by scopolamine and NMDA receptor antagonists, what is very promising for therapy but paradoxical. Although this paradox has not been rationally explained yet, three following hypotheses are postulated: (i) functional selectivity of 5-$HT_6$ ligands; (ii) regional selectivity of 5-$HT_6$ ligands; and (iii) non-selective action of tool-ligands toward 5-$HT_6$R involving other unknown protein target. All the hypotheses indicate new ligands of 5-$HT_6$R with structural diversity as the best tool to explain this paradox. Although a lot of agonists and antagonists have been found, their structural diversity is rather poor, *i.e.* more than 40% of them include indole moiety and more than 80% sulfone one [3].

In this context, our research group started to explore the totally new, non-indole and non-sulfone, chemical family of 5-$HT_6$R ligands among 1,3,5-triazine derivatives. Computer-aided design, synthesis and evaluation of pharmacological properties for the 100-member population have provided very satisfied results. The most active compounds found displayed low nanomolar affinity for 5-$HT_6$R, selectivity above 5 competitive GPCRs and strong antagonistic action in functional assays. Docking-supported SAR analysis indicated topology and chemical properties of both, the aromatic moiety and its linker to the triazine ring, as crucial factors for the affinity towards 5-$HT_6$R. Furthermore, the most active compounds showed potent procognitive action in behavioral tests *in vivo* and some anti-obesity properties. This new family of 5-$HT_6$R ligands gives wide possibilities for further pharmacomodulation and seems to be a promising perspective in order to improve the current therapy of important CNS-civilization diseases.

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# Prof. Krzysztof PALCZEWSKI

CASE WESTERN RESERVE UNIVERSITY, CLEVELAND, UNITED STATES

Dr. Krzysztof (Kris) Palczewski is an internationally recognized vision scientist and a professor at the University of California – Irvine in the Department of Ophthalmology. He is the Leopold Chair and the founding member of the Center for Translational Vision Research at Gavin Herbert Eye Institute.

His discoveries are well documented as evidenced by more than 550 scientific articles, an h-index of 111, and being cited over 43,000 times. Dr. Palczewski holds 22 patents with two of his invented drugs currently undergoing clinical trials. He has received several international awards including the 2015 Bressler Award in Vision Science and the inaugural 2014 Beckman-Argyros Award in Vision Research. He is the only scientist to win both the Cogan Award for the most promising young vision scientist (1996) and the Friedenwald Award for continuously outstanding ophthalmology research (2014). He is a recipient of Paul Kayser International Award for Retina Research from Retina Research Foundation (2018) and a member of Polish Academy of Arts and Sciences (PAU, foreign member).

# SYSTEMS PHARMACOLOGY LINKS GPCRs WITH RETINAL DEGENERATIVE DISORDERS

**Krzysztof Palczewski**

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Rhodopsin, which absorbs a photon to initiate visual phototransduction, belongs to the superfamily of G protein (guanine nucleotide-binding protein)-coupled receptors (GPCRs). Photoisomerization of the 11-cis-retinal chromophore of rhodopsin triggers a complex set of molecular events leading to light perception. Retinal photoreceptor cells can respond to light throughout our lives because they continuously regenerate a light-sensitive chromophore and certain essential structures. This series of reactions takes place in photoreceptor and the retinal pigment epithelium (RPE) cells. Defects in many proteins involved in these processes cause photoreceptor degeneration. For example, mutations in the rhodopsin gene may cause human diseases like retinitis pigmentosa (RP) that usually result in late-onset blindness. Our long-term goal is to elucidate the molecular mechanisms of phototransduction and retinal degeneration to discover therapeutics for inherited human blinding diseases caused by mutations in phototransduction genes. This is a necessary prerequisite for developing evidence-based therapeutic approaches for treatment of these pathological conditions. Combining disciplines such as state-of-the art imaging, bioinformatics, genomics, and structural biology with classical histopathological, physiological, and biochemical methods can dramatically increase understanding of causes of inherited human retinopathies.

## Dr Nurulain ZAVERI

ASTRAEA THERAPEUTICS, MOUNTAIN VIEW, UNITED STATES

Dr. Zaveri is the Founder, President and Chief Scientific Officer of Astraea Therapeutics, a preclinical discovery company she founded in 2009, whose mission is medication development for under-served diseases of the central nervous system (such as opioid and substance abuse and addiction, chronic pain and Parkinson's disease). A PhD medicinal chemist by training, Dr. Zaveri is a recognized expert in the field of G-protein coupled receptor-targeted- and ion channel-targeted drug discovery for CNS medications, that are being advanced into medication development. Before her entrepreneurial venture at Astraea Therapeutics, Dr. Zaveri was Principal Investigator and Director of the Drug Discovery Program at the Stanford Research Institute International in Menlo Park, CA, for 16 years. Dr. Zaveri is a Fellow of the American Association of Pharmaceutical Scientists (AAPS). Dr. Zaveri is the lead inventor on over 12 patents and has authored over 60 research publications and 10 reviews/book chapters in fields of her research. Dr. Zaveri also serves on several NIH grant review committees and is a long-time member of ACS and the MEDI Section.

# NEXT GENERATION PAIN THERAPEUTICS FOR THE OPIOID CRISIS: DESIGN OF BIFUNCTIONAL NOCICEPTIN/MU OPIOID GPCR LIGANDS AS NON-ADDICTING ANALGESICS

**Nurulain T. Zaveri**

*Astraea Therapeutics, Mountain View, California, USA*

The nociceptin opioid receptor (NOP, previously known as the opioid receptor-like receptor, ORL1) is well known as the 'fourth' opioid receptor, and shares significant homology with the three classical opioid receptors, mu, delta and kappa. Like the other opioid receptors, NOP is also a G-protein coupled receptor (GPCR). Its endogenous peptide ligand, nociceptin/orphaninFQ (N/OFQ), is a heptadecapeptide, which shares significant similarities with the kappa opioid peptide dynorphin, but has negligible affinity for the three classical opioid receptors.

N/OFQ and nonpeptidic small-molecule NOP agonists have been shown to modulate the pharmacology of mu opioid agonists such as morphine, particularly in pain, opioid reward and tolerance development. NOP agonists potentiate morphine analgesia at the spinal level in nonhuman primates, without potentiating the reinforcing (addictive) effects of morphine. These functional interactions led us to hypothesize that bifunctional compounds possessing NOP agonist activity and mu agonist activity may have a useful pharmacological profile, especially as non-addicting analgesics.

Different strategies may be employed to obtain 'bifunctional' activity in a single chemical entity. Two distinct pharmacophores for the two target receptors may be linked by a spacer, as has been explored previously for opioid receptor ligands. However, to obtain suitable drug-like bifunctional molecules, an ideal strategy is to develop 'integrated pharmacophores', in a single chemical scaffold. For a drug design strategy, it is a challenge to obtain and maintain the desired spectrum of activities at dual or multiple targets within a single chemical scaffold.

The NOP receptor and mu opioid receptor (MOP) share >90% homology in their transmembrane ligand binding pockets; however, none of the known MOP agonists such as morphine, show appreciable binding affinity to the NOP receptor. Therefore, to design NOP/MOP bifunctional compounds, we used rational multi-target drug design approaches, starting with NOP-selective scaffolds. Here, I will discuss the design of NOP-mu bifunctional agonists from three different chemical series, the NOP-selective dihydroindolin-2-ones, the 1,3,8-triazaspirodecanones, and the spiro-isoquinolinone class of NOP ligands. These drug design approaches for obtaining the desired bifunctional profiles were guided by structure-based drug design and optimization of SAR.

Using this strategy, we developed a novel NOP/MOP bifunctional agonist AT-121 from a NOP-selective scaffold (1). Detailed characterization of this ligand in nonhuman primates shows that AT-121 shows potent analgesia (with lower ED50 than morphine), and lacks the side effects of opioids, such as respiratory depression, abuse potential, opioid-induced hyperalgesia, physical dependence and tolerance after 30-day repeat dosing. Furthermore, AT-121 also suppresses oxycodone's reinforcing effects, at analgesic doses. Similar non-addicting and potent analgesic efficacy was also observed for other bifunctional ligands AT-200 and AT-201, from different chemical scaffolds. Such bifunctional NOP/MOP agonists with an appropriate balance of NOP and MOP agonist efficacy may provide an innovative solution for treating pain in the opioid crisis and may provide a replacement for potent, addictive opioids used for pain therapy.

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# Prof. Marcin DRAG

WROCLAV UNIVERSITY OF TECHNOLOGY, WROCLAW, POLAND

Marcin Drąg was born in Świdnica (Poland) in 1975. He earned his M.Sc. degree from Department of Chemistry at University of Wroclaw in 1999. Next, he moved to Department of Chemistry at Wroclaw University of Science and Technology, where he earned his Ph.D. in organic and bioorganic chemistry working on new inhibitors of metallo- ad cysteine proteases under supervision of prof. Pawel Kafarski. His Ph.D. thesis was awarded the best thesis in organic chemistry by Polish Chemical Society and Sigma-Aldrich (2004). In 2003 he was appointed Assistant Professor at Wroclaw University of Science and Technology and shortly after (2004) adjunct position. In years 2005-2008 he conducted postdoctoral research at The Burnham Institute for Medical Research (currently SBP Medical Discovery Institute) in La Jolla, CA (USA) in prof. Guy Salvesen laboratory. In 2011 he received Doctor of Sciences Degree in chemistry (habilitation) for work on new types of combinatorial libraries to investigate proteolytic enzymes. In 2016 he received Professor title in chemistry from President of Poland. From July 2018, prof. Drag holds also Adjunct Professor position at Sanford Burnham Prebys Medical Discovery Institute (La Jolla, California, USA). Prof. Drag supervised four Ph.D. students (all cum laude) and 5 post-docs. He is an author of more than 100 publications in per-reviewed scientific journals (for example: Nature Reviews Drug Discovery, Nature Chemical Biology, Nature Protocols, Chemical Reviews, Journal of the American Chemical Society, PNAS). His research interests in chemical biology include the design and synthesis of substrates, inhibitors and activity-based probes to decipher the mechanism of action and the function of proteases in health and disease with particular focus on use of unnatural amino acids.

# LIBRARIES OF FLUOROGENIC SUBSTRATES WITH NATURAL AND UNNATURAL AMINO ACIDS AS A TOOL IN DESIGN OF ACTIVE AND SPECIFIC PROBES FOR INVESTIGATION OF PROTEOLYTIC ENZYMES

**Marcin Drag (1), Wioletta Rut (1), Marcin Poreba (1), Katarzyna Groborz (1), Scott Snipas (2), Yoshifumi Itoh (3), Christopher Overall (4), Leszek Kaczmarek (5), Guy Salvesen (2)**

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Proteases are known to participate in many cellular processes due to their ability to process the peptide bond. They are key players in several cascades taking place in the cell with apoptosis, fibrinolysis, blood clotting, complement fixation, gastrulation or general cell cycle being only a few examples. However, proteases can be also bad guys and participate in the cellular events, which lead to severe diseases such as cancer, diabetes, pathogens infections or hypertension [1].

Each protease recognizes only substrates, which can fit into the recognition pockets. There are several methods of determination of substrate specificity [2]. Recently we have introduced Hybrid Combinatorial Substrate Library (HyCoSuL) and Counter Selection Substrate Library (CoSeSuL) for investigation of substrate specificity of endopeptidases in non-prime positions [3,4,5]. To get even better insight into substrate specificity of endopeptidases, we have applied approach with natural and unnatural amino acids for rational design of library of internally quenched substrates to investigate both prime and non-prime positions. To increase solubility and sensitivity of the assay we have also successfully introduced a new type of fluorophore and quencher pair [5]. This allowed us to obtain for several different endopeptidases much better substrates. A comparison of strategies for profiling of substrate specificity for endopeptidases will be presented.

This work was supported by the National Science Centre grant 2014/13/B/ST5/00240 in Poland.

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# Prof. Leszek KACZMAREK

NENCKI INSTITUTE OF EXPERIMENTAL BIOLOGY, WARSAW, POLAND

Leszek Kaczmarek, is a professor and head of the Laboratory of Neurobiology at the Nencki Institute, Warsaw; Poland. His major research achievements include: (i) discovery of c-Myc protein role in regulation of the cell cycle; (ii) discovery of the learning-related gene (c-fos) expression in the mammalian brain; (iii) revealing apoptotic component of excitotoxicity in the adult brain; (iv) discovery of specific role of cyclin D2 in the adult brain neurogenesis; (v) discovery of involvement of matrix metalloproteinases in neuronal plasticity, epileptogenesis, learning and memory; (vi) defining the role of the central amygdala in appetitive learning and memory. He has published over 200 research papers, cited ca. 10 000 times.

L. Kaczmarek was invited as a lecturer to more than 100 international and national meetings and over 250 times to talk on research seminars, workshops, etc.; promoted over 40 PhDs; and was PI or coordinator on over 50 domestic and international grants. He was postdoc at the Temple University (Philadelphia, USA), as well as visiting professor at the: University of Catania (Italy), McGill University (Montreal Canada), UCLA (Los Angeles, USA), Institute of Photonic Sciences, ICFO, Castelldefels, Spain. He served on numerous program and grant committees, editorial and advisory boards, as well as authorities of Polish and international scientific societies and organizations. At present he chairs the Division of Biological and Agriculture Sciences of the Polish Academy of Sciences (PAN).

Labe webpage: http://neurogene.nencki.gov.pl

# MMP-9 AT THE SYNAPSE IN THE BRAIN AND MIND

**Leszek Kaczmarek**

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Matrix metalloproteinase 9, MMP-9 is an extracellularly operating enzyme that has been demonstrated as important regulatory molecule in control of reorganization of neuronal circuitry, known as synaptic plasticity that underlies learning and memory. MMP-9 is locally produced by its mRNA translation and released from the excitatory synapses in response to neuronal activity. Extrasynaptic MMP-9 is required for growth and maturation of the dendritic spines that harbor excitatory synapses, making the synapses more efficacious. Our studies on animal models have implicated MMP-9 in such neuropsychiatric conditions, as e.g., epileptogenesis, autism spectrum disorders, development of addiction, and depression. We have also reported that in humans MMP-9 appears to contribute to epilepsy, alcohol addiction, Fragile X Syndrome, schizophrenia and bipolar disorder. In aggregate, all those conditions may be considered as relying on alterations of dendritic spines/excitatory synapses and thus understanding the role played by MMP-9 in the synaptic plasticity may allow to elucidate the underpinnings of major neuropsychiatric disorders.

## Prof. Christopher OVERALL

UNIVERSITY OF BRITISH COLUMBIA, VANCOUVER, CANADA

Professor Christopher Overall is a Tier 1 Canada Research Chair in Protease Proteomics and Systems Biology at the University of British Columbia, Vancouver, Canada, a Senior Fellow of the Freiburg Institute of Advanced Studies, Albert-Ludwigs Universität Freiburg, Germany, where he is now an Honorary Professor. He completed his undergraduate degrees in Adelaide, Australia, PhD at the University of Toronto, and Post-Doctoral training in Protein Engineering with Dr Michael Smith, Nobel Laurette. He was inducted as a fellow into the Royal Society of Canada, Academy of Science in 2018 and is Chair of the HUPO Chromosome Centric Human Proteome Project. He is best known for his development of N-Terminomic proteomic methodology for the discovery of protease substrates in vivo, thereby establishing the field of degradomics. He has used these techniques to reveal new biological roles for proteases in immunity and disease as well as new treatments to correct protease deficiency in an immunodeficiency disease. His > 270 papers have high impact with an h-index of 87.

# METALLOPROTEINASE CLEAVAGE CONTROL OF INTERFERON ALPHA AND GAMMA DAMPENS INFLAMMATION AND ANTI-VIRAL IMMUNITY

**Christopher Overall**

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In contrast to the traditional dim view of matrix metalloproteinases (MMPs) being dowdy matrix degraders, we show MMPs are protective in inflammation. We explored the roles of the immune-modulatory MMP2 and macrophage MMP12 by quantifying global proteome, protein N-termini (the N-terminome) and the altered abundance of proteases and inhibitors in inflammation. Cleavage and inactivation of the C1 inhibitor by MMP2 increased complement activation and bradykinin generation leading to increased vesselpermeability during inflammation and hence influx of acute response proteins. In exploring the role of macrophage MMP12, we found that *Mmp12-/-*mice were protected from viral endocarditis and display earlier and dramatic severe arthritis vs. wild-type mice characterized by massive neutrophil infiltrations. Overall, MMP12 is essential for INF-α section and dampens inflammation by concerted cleavages in multiple inflammation regulatory pathways. Tightly controlled macrophage differentiation and activation in the initiation and resolution of inflammation is crucial for averting progression to chronic inflammatory and autoimmune diseases. We identified a negative feedback mechanism for pro-inflammatory IFN-γ activation of macrophages driven by macrophage-associated matrix metalloproteinase 12 (MMP12). Through C-terminal truncation of IFN-γ at 135Glu↓Leu136 the IFN-γ receptor-binding site was efficiently removed, so preventing JAK-STAT1 signaling and reducing IFN-γ activation of pro-inflammatory macrophages. In an acute peritonitis model this signature was absent in*Mmp12*$^{-/-}$mice and recapitulated in *Mmp12*$^{+/+}$mice treated with a MMP12-specific inhibitor over 4 days. Similarly, loss of MMP12 led to increased IFN-γ–dependent proinflammatory markers and iNOS$^{+}$/MHC class II$^{+}$macrophage accumulation with worse lymphadenopathy, arthritic synovitis and lupus glomerulonephritis.In human systemic lupus erythematosus, MMP12 levels were lower in patients with active disease compared to treated patients or healthy subjects, and were associated with increased IFN-γ. Hence, macrophage proteolytic truncation of IFN-γ attenuates classical activation of macrophages as a prelude for resolving inflammation.

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## Prof. Aseem ANSARI

UNIVERSITY OF WISCONSIN-MADISON, MADISON, UNITED STATES

Aseem Zoe Ansari is a Professor of Chemical Genomics and Synthetic Biology at the University of Wisconsin-Madison (https://ansarilab.biochem.wisc.edu/research.html).

Professor Ansari received his Ph.D. from Northwestern University followed by postdoctoral training at Harvard University and MIT. At UW-Madison, the Ansari group creates synthetic gene regulators (SynGRs) to control stem cell fate and tackle "undruggable" genome-based diseases. Integrating chemistry, genomics, molecular medicine and bioinformatics, the Ansari group has recently created a designer gene switch that can find and fix the diseased gene that causes an incurable neuronal disease (Friedreich's ataxia). The molecular design strategy permits the precision-targeting of other genes whose malfunctions cause a wide array of diseases (Erwin et al., Science 2017).

Professor Ansari has received a few honors and awards, including: The CAREER award from the U.S. National Science Foundation (NSF), Research Excellence Award from the W. M. Keck Foundation, Basil O'Connor Starter Scholar Award from the March of Dimes Foundation, the Japan Society for Promotion of Science (JSPS) fellowship, the Resident Tutorship at Winthrop House from Harvard, and the first prize for graduate research from Sigma Xi Research society at Northwestern.

# DESIGNING SYNTHETIC GENE REGULATORS (SYNGR)

**Aseem Ansari**

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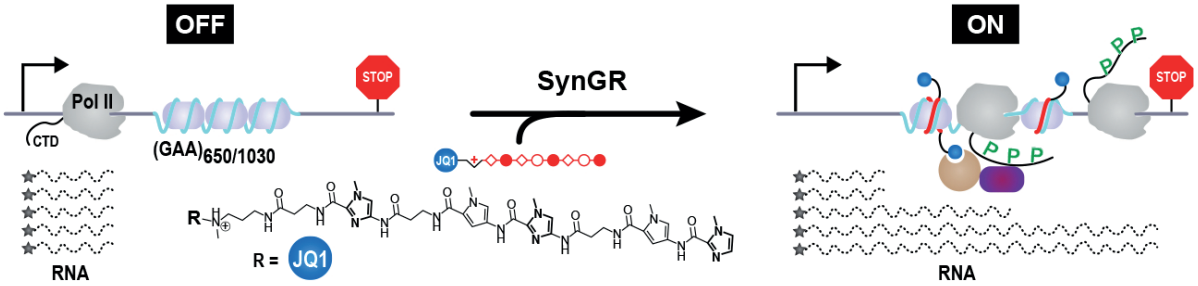
To target desired genomic loci in vivo, we use the *polyamide* class of small molecule DNA binders. These imidazole/pyrrole based molecules can be rationally designed to target desired sequences in the genome. To the polyamide scaffold, we conjugate specific ligands that engage specific cellular machines to modify local epigenetic/chromatin states and regulate the expression of targeted genes. We recently created a SynGR (SynTEF1) to enable transcription across the repressive GAA repeats that cause Friedreich's ataxia, a lethal neurodegenerative disease.

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# Prof. Alessandra S. EUSTAQUIO

UNIVERSITY OF ILLINOIS AT CHICAGO, CHICAGO, UNITED STATES

**Alessandra S. Eustaquio, Assistant Professor, Medicinal Chemistry and Pharmacognosy**

Dr. Eustaquio has been an Assistant Professor in the Department of Medicinal Chemistry and Pharmacognosy of the University of Illinois at Chicago (UIC) since August 2015. She also holds an appointment with the Center for Biomolecular Sciences. The Eustaquio laboratory aims to contribute to drug discovery and development from natural products. Bacterial metabolites account for the majority of antibiotics in use in the clinic today. The Eustaquio lab uses open-source bioinformatics tools to predict the biosynthetic potential of bacteria based on their genome sequences (genome mining). We then carry out genetic engineering to activate expression of silent genes and obtain the encoded antibiotics. We are also interested in understanding antibiotic biosynthesis and transcriptional regulation. Finally, we are interested in developing synthetic biology tools to facilitate access to natural and engineered compounds.

Before joining UIC, Dr. Eustaquio was a Principal Scientist at Pfizer, Medicinal Chemistry, Natural Products group. Prior to that, she had done postdoctoral training at the University of California San Diego, obtained a PhD in Pharmaceutical Biology from the University of Tuebingen, Germany, and a B.Sc. in Pharmacy & Biochemistry from the University of São Paulo, Brazil.

# EXPLORING BACTERIAL GENOMES FOR NATURAL PRODUCT DISCOVERY AND DEVELOPMENT

**Alessandra Eustaquio**

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Despite deprioritization of natural products research by the private sector in the early 1990s, natural products continue to yield new drugs. The main advantage of natural products as a source of drugs – they have evolved to interact with biological systems and, thus, hit rates are higher than with synthetic molecules – makes it worthwhile to overcome their intrinsic challenges. During the discovery stage, the rediscovery of known compounds is the main challenge. Once a natural product hit has been identified, supply issues and difficulties with structure diversification may hinder development. A continued understanding of natural product biosynthesis coupled with genomic and synthetic biology approaches can contribute to overcoming these challenges. In this presentation, I will provide examples of genome mining to identify biosynthetic genes (1-3), and will discuss how that knowledge can be used to increase supply (4), and to contribute to structure diversification. Finally, I will discuss our efforts toward developing synthetic biology tools to facilitate natural product discovery (5).

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# Dr Mathias FREDERIKSEN

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH (NIBR),
BASEL, SWITZERLAND

Mathias Frederiksen obtained his PhD from Imperial College in London in 2003 under the mentorship of Professor Tony Barrett. He then moved to Stanford University to pursue post-doctoral studies with Professor Barry Trost.

He joined Novartis Institutes of Biomedical Research in 2005 as a medicinal chemist in the Neuroscience department. In 2010 he started the Chemical Genetics group in Basel with a focus on target discovery and validation using phenotypic screens. In late 2017 he transitioned to his current role as group leader for the Chromatin Chemical Biology Group, where the focus is now on contextualizing and understanding the non-coding genome and rendering it accessible for drug discovery.

# INTEGRATIVE SCREENING IDENTIFIES A NOVEL NODE IN THE ONCOGENIC YAP/HIPPO PATHWAY

**Mathias Frederiksen**

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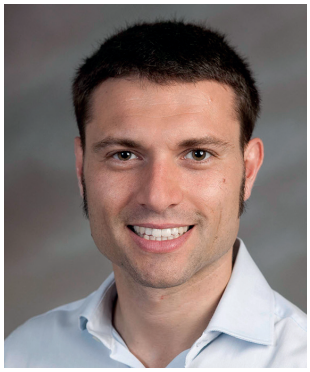
Genomics in Drug Discovery; what is the role for chemistry? Indeed, an intriguing question! We are now firmly in the era of genome-wide genetic target discovery screens and one could be inclined to think that the role for chemistry and chemical genetics has been relegated to a discipline of the past. In this seminar we will discuss how, quite to the contrary, chemistry has a pivotal role to play in this space. Using an integrated target discovery approach in the context of the YAP-Hippo pathway as an example, we demonstrate how, by careful design, the genetic screens and LMW screens inform each other and dramatically accelerate target discovery and validation.



# Prof. Alessio CIULLI

UNIVERSITY OF DUNDEE, DUNDEE, UNITED KINGDOM

Alessio Ciulli holds the Personal Chair of Chemical and Structural Biology at the School of Life Sciences, University of Dundee. His research interests are in chemical biology, structural biology and drug discovery of protein-protein interactions (PPIs) within the chromatin and ubiquitin-proteasome systems. Of particular interest are the development and application of small molecules approaches for inducing protein degradation, and chemical genetics and fragment based drug design approaches to target protein surfaces and PPIs.

Alessio graduated in Chemistry (2002) from his hometown Florence under the late Ivano Bertini and obtained his PhD from the University of Cambridge (Chemistry, 2006), studying as a Gates Cambridge Scholar under the supervision of Chris Abell and in collaboration with Astex Pharmaceuticals. Following post-doctoral research on fragment-based drug design with Chris Abell and Tom Blundell, and an HFSP visiting Fellowship at Yale University to begin collaboration with Craig Crews (2009), he was awarded a BBSRC David Phillips Fellowship and returned to Cambridge to start his independent career in 2010. In 2013 Alessio was awarded an ERC Starting Grant and moved his laboratory to the School of Life Sciences at Dundee to take up a Readership and Principal Investigator role within the Division of Biological Chemistry and Drug Discovery. He was promoted to Professor in October 2016. He is a Fellow of the Royal Society of Chemistry. Alessio is the recipient of several prizes and awards, including:

- 2014 Talented Young Italian award
- 2015 EFMC Prize for Young Medicinal Chemist in Academia
- 2015 ICBS Young Chemical Biologist Award
- 2016 RSC Capps Green Zomaya Award in medicinal computational chemistry
- 2016 MedChemComm Emerging Investigator Lectureship.

# TARGETED PROTEIN DEGRADATION WITH SMALL MOLECULES: HOW PROTACS WORK

**Alessio Ciulli**

*School of Life Sciences, Division of Biological Chemistry and Drug Discovery University of Dundee*

Bivalent degrader molecules (also termed PROTACs) are a revolutionary new modality class with therapeutic potential. PROTACs target proteins for degradation through recruitment to E3 ligases. Formation of a ternary complex between the degrader, the ligase and the target leads to the tagging by ubiquitination and proteasomal degradation of the target protein.

In recent years my Lab has contributed to illuminate fundamental structural and biophysical insights into PROTAC molecular recognition and mechanism of action. In 2015, we disclosed MZ1, a potent degrader made of a ligand we had previously discovered for the E3 ligase von Hippel-Lindau (VHL), and a pan-selective ligand for the BET proteins Brd2, Brd3 and Brd4. We made the unexpected but fascinating observation that MZ1 induces preferential degradation of Brd4 over Brd2 and Brd3 - despite engaging BET proteins with comparable binary binding affinity. In 2017 we published the first crystal structure of a PROTAC ternary complex (VHL:MZ1:Brd4) which illuminated the role of cooperative molecular recognition inducing *de novo* contacts to form a stable ternary. More recently, we developed a new assay based on surface plasmon resonance (SPR) and showed that long-lived ternary complexes drive PROTAC-mediated protein degradation.

Together these studies contribute to elucidate important guiding principles of how PROTACs work.

# Prof. Huib OVAA

LEIDEN UNIVERSITY MEDICAL CENTER, LEIDEN, THE NETHERLANDS

**Huib Ovaa, Professor Leiden University Medical Center, Department of Cell and Chemical Biology, Leiden, the Netherlands**

Education/training: Maters's 01-07-1997, studies Chemistry, Main subject Organic Synthesis, Leiden University the Netherlands. Doctorate/PhD 03-10-2001 Phd, title of thesis 'Synthetic Organic Chemistry', supervisor J.H. van Boom/H.S. Overkleeft, Leiden University the Netherlands.

Positions and employment: 2015-present: Professor Leiden University Medical Center; 2016-present: Professor Leiden University; 2016-present Guest Researcher Netherlands Cancer Institute (NKI); 2012-2016: Extraordinary Professor Leiden University; 2010-2013:0.1FTE C.S.O. UbiQ Bio B.V.; 2009-2016: Tenured staff member Netherlands Cancer Institute (NKI); 2005-2012: Assistant Professor, Leiden University, the Netherlands; 2004-2009: Junior group leader, Netherlands Cancer Institute (NKI); 2004-2005: Guest Researcher, Leiden University; 2003-2004: Instructor in Pathology, Harvard Medical School, Boston, U.S.A.; 2001-2003: Post-doctoral fellow, Harvard Medical School, Boston U.S.A.

Research Field: Chemical Biology. My group specializes in the development of novel techniques to profile cellular enzymatic activities associated primarily with ubiquitin-mediated proteasomal degradation and antigen presentation. We use an organic synthesis driven approach in order to gain further understanding of the cellular processes under investigation by preparing small molecule-activity modulators and synthetic protein- reporters on enzymatic activities by both rational design and by en masse screening of small molecule libraries followed by hit-optimization and subsequent development of research tools.

# THE UBIQUITIN SYSTEM

**Huib Ovaa**

*Oncode Institute, Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, the Netherlands*

Modification of proteins with ubiquitin and ubiquitin-like proteins regulates a plethora of cellular events, ranging from DNA repair to proteolysis and intracellular trafficking. This lecture will deal with methods to chemically synthesize such proteins and discusses how to use them in structural, biochemical and cell biological studies with a range of examples.

References

1) Liu H. Y., Wan X. J., Yao Y. W., et al., Sens. Actuator B: Chem. 2014, 200, 191-197

# Dr Yves P. AUBERSON

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH,
BASEL, SWITZERLAND

Yves P. Auberson obtained his Ph.D. in 1990 at the Swiss Federal Institute of Technology in Lausanne, Switzerland. He joined the Novartis Institute for BioMedical Research in Basel, Switzerland in 1992, after a post-doctoral training in chemical biology at Affymax in Palo Alto, USA.

He is currently Executive Director in Global Discovery Chemistry, where his research group develops tracers for clinical imaging. Previously, he was Head of Chemistry for Neuroscience, and played a leading role in the discovery and development of drug candidates for the treatment of epilepsy, Alzheimer's disease and narcolepsy.

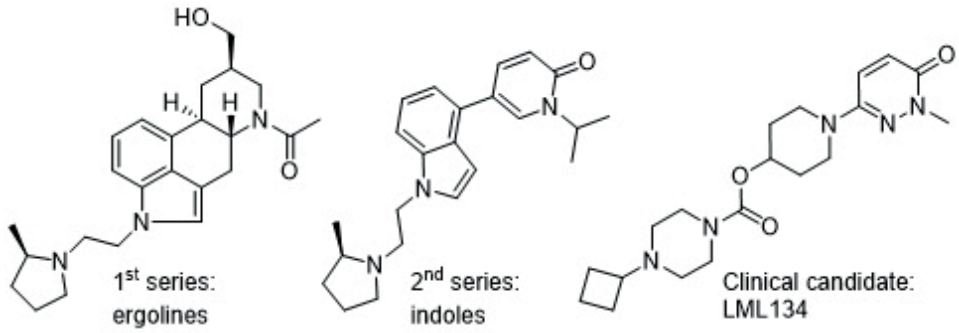
He is President of the European Federation of Medicinal Chemistry (EFMC), and of the Division of Medicinal Chemistry and Chemical Biology of the Swiss Chemical Society.

# THE DISCOVERY OF LML134, A HISTAMINE H3 RECEPTOR INVERSE AGONIST FOR THE CLINICAL TREATMENT OF EXCESSIVE SLEEP DISORDERS

**Yves P. Auberson**

*Novartis Institutes for Biomedical Research, Basel, Switzerland*

Histamine 3 receptor (H3R) inverse agonists that have been in clinical trials for treatment of excessive sleep disorders have been plagued with insomnia as a mechanism-based side effect. We focused on identifying compounds that achieve high receptor occupancy within a short time after oral administration, followed by fast disengagement from the receptor, a target profile that could provide the therapeutic benefits without the undesired insomnia side effect. This presentation describes the optimization work that led to the evaluation of three independent chemical series, and ultimately to the discovery of the clinical development candidate 1-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)piperidin-4-yl 4-cyclobutylpiperazine-1-carboxylate (LML134).



# Dr Chris TATE

MRC LABORATORY OF MOLECULAR BIOLOGY,
CAMBRIDGE, UNITED KINGDOM

Chris obtained his PhD from the University of Bristol (1989) and then moved to the University of Cambridge (Dept of Biochemistry). After obtaining a research fellowship at Girton College (Cambridge) he moved to the LMB to work in Richard Henderson's group on the serotonin transporter. Chris then worked on the E. coli multidrug transporter EmrE and obtained both 2D and 3D crystals as well as a 3D structure using cryo-EM. In 2005 he started working on the development of conformational thermostabilisation of GPCRs, which resulted in the structure of the β1-adrenoceptor. Subsequent work has focused on understanding the molecular basis of GPCR pharmacology through structure determination of the β1-adrenoceptor and adenosine A2A receptor in multiple different conformations bound to ligands of different efficacy. In 2016 mini-G proteins were developed as a tool for the structure determination of GPCRs in the fully active state. Structures have been determined either by X-ray crystallography of receptors coupled to either mini-Gs or mini-Go, or by electron cryo-microscopy of receptors coupled to mini G protein bound to ββ subunits.

# G PROTEIN-COUPLED RECEPTORS: THE STRUCTURAL BASIS FOR THEIR PHARMACOLOGY

**Christopher Tate**

*MRC Laboratory of Molecular Biology, Francis Crisk Avenue, Cambridge CB2 0QH, UK*

G protein-coupled receptors (GPCRs) activate intracellular signalling proteins (G proteins and arrestins) in response to extracellular signalling molecules. GPCRs are highly dynamic proteins, which rapidly interchange between different conformational states. In order to understand the molecular mechanisms of GPCR activation, structures of GPCRs in different conformational states are required.

We have determined structures of the adenosine $A_{2a}$ receptor ($A_{2a}R$) and $b_1$ adrenoceptor ($b_1AR$) in a variety of different states bound to ligands ranging from inverse agonists to full agonists. Structures in active states have also been determined of $A_{2a}R$ and the serotonin 5-$HT_{1B}$ receptor coupled to the heterotrimeric G proteins $G_s$ and $G_o$, respectively. I will use this wealth of structural data to address a number of questions with respect to GPCR pharmacology such as why do G proteins cause an increase in agonist affinity and what are the factors that affect the specificity of G protein coupling.

References

1) García-Nafría, J., Lee, Y., Bai, X., Carpenter, B. & Tate, C.G. (2018) Cryo-EM structure of the adenosine A2A receptor coupled to an engineered heterotrimeric G protein. eLife 7, e35946
2) García-Nafría, J., Nehmé, R., Edwards, P.C. & Tate, C.G. (2018) Cryo-EM structure of the serotonin 5-HT1B receptor coupled to heterotrimeric Go. Nature 558, 620-623.
3) Warne, T., Edwards, P.C. Doré, A.S., Leslie, A.G.W. & Tate, C.G. (2018) Molecular diversity of high affinity agonist binding in active states of the β1-adrenoceptor. Submitted.

# Dr Uta LESSEL

BOEHRINGER INGELHEIM, BIBERACH AN DER RISS, GERMANY

Uta Lessel, Principal Scientist in Computational Chemistry within the Department Medicinal Chemistry

Working on early projects (special fields of interest: virtual screening, phenotypic screening and macrocycles)

Study of Pharmaceutical sciences at the University of Düsseldorf

PhD in Pharmaceutical Chemistry from the University of Düsseldorf

Postdoc at a research institute in Brunswick (Germany) and at the University of Cologne

Joined Boehringer Ingelheim in 1998

# DESIGN OF OREXIN 1 RECEPTOR SELECTIVE ANTAGONISTS

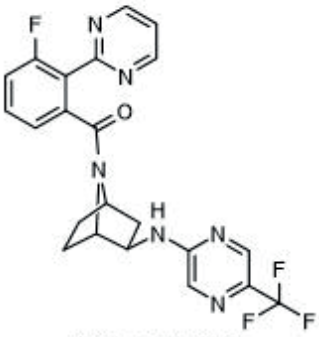
**Uta Lessel, Doris Riether, Marco Ferrara, Niklas Heine, Chiara Marelli, Laura Carrettoni, Roland Pfau**

*Boehringer-Ingelheim Pharma GmbH & Co. KG, Biberach, Germany*

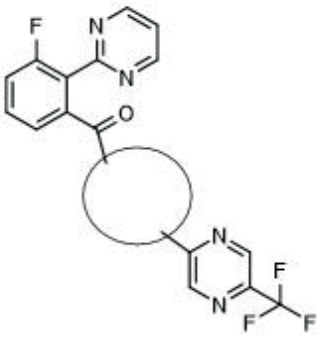
Orexine 1 receptor (OX1R) antagonists are of interest for treating disorders related to impulse control deficits as seen in addictions such as substance use disorders, personality disorders, eating disorders or attention deficit hyperactivity disorder. Due to the sleep-inducing effect of Orexine 2 receptor (OXR2) inhibition dual OX1R and OX2R antagonists are not suitable and selectivity over OX2R is necessary.

Here we will present the design of highly selective OX1R antagonists based on the crystal structures of OXRs in complex with the dual OX1R/OX2R antagonist Suvorexant. By comparison of the X-ray structures we postulated which regions of the OXR pockets are responsible for selectivity. Based on a binding mode hypothesis for moderately selective OX1R antagonists with a [2.2.1]-bicycle as in JNJ-54717793[1], which served as our starting point, we proposed structural changes in parts of the scaffold pointing to the region that is potentially decisive for selectivity. These structural variations led to a modified core with inherently higher selectivity compared to the [2.2.1]-bicycle template.

We will discuss the structure-based design, synthesis, and hit-to-lead evaluation of this novel OX1R selective scaffold.



JNJ-54717793
OX1R selectivity = 67-fold



OX1R selectivity = 280-fold

References

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# Dr Lothar SCHWINK

SANOFI, FRANKFURT AM MAIN, GERMANY

Lothar Schwink, Dr. rer. nat.

Head of Laboratory, Sanofi-Aventis Deutschland GmbH (Frankfurt, Germany)

Lothar studied chemistry at the Philipps-University in Marburg (Germany) were he earned his doctoral degree for his work on asymmetric catalysis under the supervision of Prof. Paul Knochel in 1997. During a postdoctoral stay at the University of California, Irvine, in Prof. Larry Overman's group, he completed the total synthesis of aloperine and succeeded in assembling a strategic intermediate for asparagamine A.

Since 1999, Lothar is leading research teams directed towards the optimization of small molecule drug candidates for metabolic diseases at Sanofi or its predecessor companies. Examples include natural product derived enzyme inhibitors, and several modulators of nuclear hormone and G-protein coupled receptors.

# NEXT GENERATION GPR119 AGONISTS AS POTENTIAL TREATMENT FOR CARDIOMETABOLIC DISEASES

**Jens Atzrodt, Christian Buning, Andreas Czich, Heiner Glombik, Nis Halland, Thomas Kissner, Eckart Krupp, Matthias Lohmann, Peter Monecke, Tobias Paehler, Christoph Poeverlein, Markus Rehberg, Kurt Ritter, Matthias Schaefer, Lothar Schwink**

*Sanofi-Aventis Deutschland GmbH, R&D Integrated Drug Discover, Industriepark Hoechst - Bldg. G838, 65926 Frankfurt am Main, Germany*

Despite the current widespread use of statins to lower the "bad" cholesterol (LDL-C) the residual risk for major adverse cardiovascular events like CV death, myocardial infarction (MI) and stroke remains high. This is especially true for type 2 diabetic patients. They often show –alongside elevated blood glucose (BG) levels- a strongly atherogenic mixed dyslipidemia characterized by high triglyceride (TG) and small dense LDL particle levels, whereas the "good" cholesterol (HDL-C) level is reduced, resulting in a 3-4 fold increased CV-risk. Thus, in view of the ongoing diabetes pandemic (~629 million patients by 2045, ~70% threatened by premature death mostly due to MI and stroke), drugs that minimize excess CV morbidity/mortality are urgently needed. [1-2]

Activation of the G-protein coupled receptor 119 (GPR119) at its two major sites of expression (gut and pancreas) enhances gut hormone (e.g. GLP-1, GIP, PYY) secretion and potentiates glucose stimulated insulin release, thereby addressing all hallmarks of diabetic dyslipidemia (i.e. reduction of BG, TGs and LDL-C together with elevation of HDL-C) by a mechanism that is orthogonal to statins. But, so far, clinical development of GPR119 agonists has been hampered by a perceived lack of sufficient efficacy, limiting physicochemical/PK properties and/or safety signals. [3]

Herein we present our efforts to optimize the efficacy and safety profile in a series of GPR119 agonists featuring a pyrrolidinone central scaffold. Candidate selection was mainly based on high intrinsic receptor activation across species and the use of novel biomarkers to dial out organ (kidney) toxicity liabilities even in the absence of histological findings in exploratory in vivo toxicity studies.

References

1) IDF DIABETES ATLAS, Eighth edition 2017
2) D. L. Bhatt et al., N Engl J Med 2019, 380, 11-22
3) K. Ritter et al., J Med Chem 2016, 59, 3579-3592

## Prof. Maria Laura BOLOGNESI

UNIVERSITY OF BOLOGNA, BOLOGNA, ITALY

Maria Laura Bolognesi holds the position of Professor of Medicinal Chemistry and Director of the Chemistry and Pharmaceutical Technologies degree program at the Alma Mater Studiorum - University of Bologna. She received her PhD in Pharmaceutical Sciences in 1996 and carried out postdoctoral work at the University of Minnesota. Her research explores the development of small molecules in the neurodegenerative and neglected tropical disease therapeutic areas. Maria Laura has a track record of more than 160 publications in high-ranked scientific journals, including patents and patent applications, and numerous invited talks worldwide. She 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 also an Associate Editor of Journal of Medicinal Chemistry and serves in the Advisory Board of the European Federation of Medicinal Chemistry.

# CHARTING NEW PATHS IN MULTI-TARGET DRUG DISCOVERY FOR ALZHEIMER'S DISEASE

**Maria-Laura Bolognesi**

*Department of Pharmacy and Biotechnology, Alma Mater Studiorum - University of Bologna, Via Belmeloro 6, I-40126 Bologna, Italy*

In the last ten years the concept of multitarget-directed ligands (MTDLs) to combat Alzheimer's diseases has garnered great attention.[1] Since the 2000, medicinal chemists have applied multi-target concepts in various forms and with varying degrees of success to the design of compounds able to simultaneously hit several targets. Although we have been very prolific, many of the performed approaches have yet to bear fruit in terms of candidates being progressed to clinical trials. Undoubtedly, AD multitarget drug discovery combines the hurdles of an extremely challenging area with those of novel pharmaceutical tools. However, we cannot ignore critical issues that might hamper translational success.[2] First, too many newly reported MTDLs are "follow-on" compounds, with high chemical structure similarity and directed to the same target combinations, without adding therapeutic value. Second, we have been over-reliant on the hybrid drug design approach, sometimes overlooking that framework combination might lead to large dual ligands, with unfavorable CNS-like properties. Last, but not least, to develop clinically effective MTDLs, the selection of appropriate targets is of utmost importance. They should be causally linked to the most relevant AD pathological processes, and their "networking" is critical for determining the final properties of the MTDL.

With all these concepts in mind, we have recently identified novel small molecules MTDLs that hit tau cascade at two validated hubs, namely by inhibiting glycogen synthase kinase 3β (GSK-3β) and the tau aggregation process. Although in principle very promising, this approach has to deal with the peculiar problem of targeting two proteins with no binding site similarity. In this lecture, we will discuss why and how multi-target drug discovery concepts have been exploited to identify the first-in-class chemical series of dual GSK-3β/tau aggregation inhibitors.

References

1) Cavalli, A., Bolognesi, M. L., Minarini, A., Rosini, M., Tumiatti, V., Recanatini, M., Melchiorre, C. Multi-target-directed ligands to combat neurodegenerative diseases. J. Med. Chem, 2008, 51, 347-372.
2) Bolognesi, M. L. Harnessing Polypharmacology with Medicinal Chemistry. ACS Med. Chem. Lett. 2019, acsmedchemlett.9b00039.

# Prof. Holger STARK

HEINRICH HEINE UNIVERSITY DÜSSELDORF,
DUESSELDORF, GERMANY

Prof. Dr. Dr. h.c.Holger Stark studied pharmacy and finished his PhD in Medicinal Chemistry at the Free University of Berlin. He focused on neurotransmitter research with emphasis on histamine as well as dopamine receptor subtypes and expanded this on lipid signalling. In 2000 he became full professor at the Goethe University in Frankfurt, Germany and went in 2013 to the Heinrich Heine University in Düsseldorf, Germany where he has his actual position. He founded some start-up companies on cancer therapeutics (Warburg Glycomed, PSites Pharma) and has received several prices for his successful research as well as for teaching. He is co-inventor of pitolisant (Wakix®), the first histamine H3 receptor antagonist with market approval, and has prepared some back-up candidates in different leads for various targets. Since 2004 Holger Stark is editor-in-chief of the Archiv der Pharmazie – Chemistry in Life Sciences, one of the oldest journals on Medicinal Chemistry.

# MULTIPLE TARGETING - THE HISTAMINE H3 RECEPTOR PHARMACOPHORE AS CENTRAL ELEMENT

**Holger Stark**

*Heinrich Heine University Düsseldorf, Institute of Pharmaceutical and Medicinal Chemistry, Universitaetsstr. 1, 40225 Duesseldorf, Germany; E-mail: stark@hhu.de*

The concept of drug design has changed in many aspects from Paul Ehrlich´s “magic bullet” to some multi-targeting approaches named as “magic shotgun”. Addressing more than one target in one drug seems especially attractive in neurodegenerative disease in which multiple causes have been detected and a high medical need for new medications have been described. Whereas this approach has sometimes been achieved by serendipity, the rational structural design based on the understanding of the disease as well as on the structure-activity relationships (SAR) are the more successful steps in drug development.
Pitolisant, the first antagonist/inverse agonist at histamine H3 receptor (H3R) with market approval in Europe, has shown numeral influences of other neurotransmitters and a robust pharmacophore. With optimization of pharmacodynamics properties, numerous other pharmacophores can be introduced maintaining affinities [1]. We have started with multiple enzyme inhibitions simultaneously to H3R inhibition more than a decade ago [2]. Recently, we updated this strategy with a straight forward overlapping combination of the G-protein coupled H3R pharmacophore with enzyme inhibition properties at monoamine oxidase B (MAO B) [3]. The complex SAR in different pharmacological classes combined in a small molecule needs a thorough understanding of each aspect. This has been demonstrated in the development of contilisant as inhibitor of H3R, MAO B as well as cholinesterases with procognitive effects in vivo [4].

The multiple targeting approach is also the main topic of the EU COST Action CA15135 MuTaLig for academia and industry with multiple research competences (www.mutalig.eu).

References

1) M. A. Khanfar et al. Multiple Targeting Approaches on Histamine H3 Receptor Antagonists. Front. Neurosci. 2016, 10, 201; doi: 10.3389/fnins.2016.00201.
2) G. Petrianou et al. Multiple Enzyme Inhibitions of Histamine H3 Receptor Antagonists as Potential Procognitive Agents. Pharmazie 2006, 61, 179-182
3) A. Affini at el. Novel Indanone Derivatives as MAO B/H3R Dual Targeting Ligands for Treatment of Parkinson´s Disease. Eur. J. Med. Chem. 2018, 148, 487-497.
4) Ó. M. Bautista-Aguilera et al. Multitarget-Directed Ligands Combining Cholinesterase and Monoamine Oxidase Inhibition with Histamine H3R Antagonism for Neurodegenerative Diseases. Angew. Chem. Int. Ed. 2017, 56, 12765-12769.

# Prof. Katarzyna STAROWICZ-BUBAK

INSTITUTE OF PHARMACOLOGY, POLISH ACADEMY OF SCIENCES, KRAKOW, POLAND

Katarzyna Starowicz (PhD, DSc) is a neuropharmacologist leading Department of Neurochemistry based at the Institute of Pharmacology Polish Academy of Sciences (www.if-pan.krakow.pl).

her education includes M.Sc. degree in Biotechnology from the Jagiellonian University (2000), PhD in Pharmacology at the Medical Sciences at the Utrecht University (2005) and Habilitation in Medical Biology at the Faculty of Medicine of the Jagiellonian University Medical College (2013). After receiving a PhD degree she started a postdoctoral fellowship in Endocannabinoid Research Group under the supervision of prof. Vincenzo Di Marzo. After completing the postdoctoral fellowship she returned to Poland where she have established and maintained a laboratory focused on understanding of the mechanisms of chronic pain and on the characteristics of endogenous system involved in the transmission of pain stimuli with particular attention to endocannabinoid system. Subsequently, my research interests expanded to include the issue of degenerative joint disease (particularly osteoarthritis, OA).

Please visit http://www.painlab.pl for more details and full description of current research interests.

Laureate of the Powroty / Homing program of the Foundation for Polish Science, the habilitation scholarship of L'Oréal Poland for Women and Science in 2012 and the National Science Centre Award in Life Science in 2016. Member of British Journal of Pharmacology Editorial Board. President of the Alumni Association of the Foundation for Polish Science (2017-2019). V-ce President of the Board of National Agency for Academic Exchage (NAWA, www.nawa.gov.pl).

# CANNABINOID RECEPTOR TYPE 2 MODULATION TO IMPROVE OUTCOMES FOR CARTILAGE REPAIR IN THE OSTEOARTHRITIC JOINT

**Jakub Mlost, Przemysław Kac , Marta Bryk, Katarzyna Starowicz**

*Institute of Pharmacology, Polish Academy of Sciences, Department of Neurochemistry, 12 Smetna, 31-343 Krakow, Poland*

Osteoarthritis (OA) is the most common degenerative joint disease, characterized i.e. by gradual destruction of articular cartilage, exposure of innervated subchondral bone, which leads to pain during joint loading and chronic physical disability. The hallmark symptom of osteoarthritis is pain. Pain relief remains a primary unmet medical need with issues around safety and tolerability, and enhanced efficacy. In addition, the elderly, osteoarthritis population usually presents several comorbidities increasing the risk for drug-drug interactions and the occurrence of serious adverse events. Because of these limitations, pain is poorly controlled.

Compelling evidence suggests an active participation of the endocannabinoid (EC) system in the pathophysiology of joint pain associated with OA. Regardless of the analgesic properties of potent and selective FAAH (fatty acid amide hydrolase) inhibitors in rodent pain models they have treatment limitations and failed in clinical trials. The attention now focuses on the crucial functional role of CB2 receptor in the regulation of chronic joint pain further supporting the potential interest of CB2 agonists. Thus the aim of our studies is to characterize the anti-inflammatory and antinociceptive potential CB2 receptors agonists as a pain target, in search for novel pain treatment.

We evaluated therapeutic potential of three functionally biased CB2 agonists in order to establish the most beneficial treatment strategy for OA. Recent data implies significant role of functional selectivity upon signal transduction pathways that may increase beneficial properties while reducing side effects. JWH133 (as cAMP biased agonist), GW833972A (as β-arrestin biased agonist) and dietary compound β-caryophyllene (BCP, as low efficacy agonist) were used in different treatment regimens in order to propose the best pharmacological approach for OA management.

Behavioural evaluations were carried out 1 hour after i.p. treatment with CB2 agonist. Pressure Application Measurement (PAM, UgoBasile) was used for joint pain assessment, Kinetic Weight Bearing instrument (KWB, Bioseb) was used for measuring gait characteristics of freely moving animal. Patients living with OA often exhibit abnormal movement patterns primarily due to altered joint kinematics. While some of these gait changes in OA are due to deterioration in joint congruency, compensatory movement to minimize joint loading and pain is also likely to play a part. This is why monitoring animal movement following arthritis induction could reveal some interesting insights into pain perception. Among 20 available parameters measured by KWB - peak force, peak surface, swing duration and ratio of swing to laid duration phase of rear paws were selected for further analysis.

All CB2 agonists exerted anti-nociceptive effects following acute administration, whereas in chronic treatment regimen, we observed tolerance related to both β-arrestin pathway specific and high efficacy. High efficacy and β-arrestin selective, GW833972A exerted most pronounced tolerance, as seen by decline in its anti-nociceptive effects in all measured parameters, whereas some of JWH133, a high efficacy and cAMP selective agonists, effects remained constant throughout the course of the experiment. BCP, a natural and low-efficacy CB2 agonist, has exerted the least pronounced decrease in antinociceptive potential in all measured parameters. What is more, histological staining revealed improvement in cartilage degeneration scores following chronic CB2 agonists treatment, however microtomography has not detected any significant changes in subchondral bone architecture due to JWH133 treatment. These results imply functional selectivity as not only, a key factor in predicting clinical usefulness of drugs but also as a significant confounding variable in basic research.

This study suggests a range of potential future applications based on Cb2 agonists like identification and validation of novel drug targets among cannabinoids and potential alternative therapy for chronic pain sufferers. Most importantly, our results present significant impact of signalling bias and efficacy upon analgesic potential of CB2 agonists.

Supported by National Science Centre, Poland by grants: OPUS no. 2014/13/B/NZ7/02311, 2015-2018 and statutory funds.

# Prof. Rafael FRANCO

UNIVERSITY OF BARCELONA, BARCELONA, SPAIN

Rafael Franco (PhD). Present position: Full professor of Biochemistry and Molecular Biology. rfranco@ub.edu; rfranco123@gmail.com. Mobile +34610306123

Affiliation 1: Department of Biochemistry and Molecular Biomedicine. University of Barcelona. Barcelona. Spain

Affiliation 2. Network Center for Neurodegenerative Research (CiberNed). Instituto Carlos III. Madrid. Spain.

I am Molecular Neuropharmacologist coming with Biochemistry and Molecular Biology background.

I did a first postdoc stay in the lab of Prof. Geoffrey Burnstock in UCL (Univ College London) where I get acquainted with purinergic nerves and purinergic actions.

Back in Spain I founded one of the first labs in Europe devoted to the work from a molecular point of view of G protein-coupled receptors (GPCRs).

Other stays abroad were: in Max Planck Institute Dortmund with Prof. Rolk Kinne, in Harvard Medical School with Prof. Cox Terhorst and in Pasteur Institute with Prof. Ara Hovanessian.

My laboratory is internationally known for the discovery of GPCR heteromers and for research on their physiological relevance.

The main focus is the central nervous system and we now have taken a translational approach for which we collaborate with Medicinal Chemistry laboratories in different Countries.

GPCRs in our portfolio include, among other, those for adenosine, cannabinoids, epinephrine, orexin, dopamine and ghrelin.

We are interested in neurodegenerative diseases and in drug addiction (cocaine, ethanol and amphetamine)

I have circa 400 papers mainly in international journal and h index as of Nov 2018 is: 68.

Number of citations is >15,000.

# POTENTIAL OF NATURAL CANNABINOIDS AND SYNTHETIC CANNABINOIDS IN NEUROPROTECTION

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The endocannabinoid system is composed of two main endocannabinoids (anandamide and 2-Arachidonoylglycerol), the enzymes that synthesize and degrade them and two cannabinoid (CB1 and CB2) receptors. Unlike other natural products derived from plants containing drug-addictive molecules, cannabinoids did not attract much attention from a therapeutic point of view. Matters changed when rimonabant, an antagonist of one of the two existing cannabinoid receptors (CB1), was approved for weight loss. Unfortunately, the drug was banned due to serious side effects. Recent data on cannabinoid research together with approval of drugs containing *Cannabis sativa* extracts (Sativex®) and cannabidiol (Epidiolex®) leads to very promising prospects for natural and synthetic cannabinoids in therapy. This presentation will provide data on the relevant role of cannabinoid receptors in microglia to combat neuronal death (Navarro et al. 2018) and will concentrate on molecules acting on CB2 receptors whose activation by agonists do not cause psychotropic effects. Recent data in the laboratory (Martínez-Pinilla et al. 2017) plus recent elucidation of the CB2R 3D structure (Li et al. 2019) has lead to the identification of centers other than the orthosteric one. Biased agonism, allosteric modulation (Morales et al. 2018) and effects of bitopic ligands on CB2 receptors will be presented. Taken together, existing data suggest that allosteric and/or bitopic CB2 compounds may progress toward clinical trials aimed at assessing efficacy against neurodegenerative diseases.

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## Dr Marc NAZARE

FMP, BERLIN, GERMANY

Marc Nazare is a group leader medicinal chemistry at the Leibniz Institut fuer Molekulare Pharmakologie FMP, Berlin, Germany. He studied chemistry at the University of Karlsruhe and obtained his PhD in organic chemistry in 1999 under the guidance of Prof. Herbert Waldmann working on a natural product total synthesis. He started his career in the pharmaceutical industry at Aventis (now Sanofi) in Frankfurt, as a medicinal chemist and project leader. Over the years he has been working on kinase-, GPCR-, protease- and ion channel projects covering both early and late stage research. Marc Nazare contributed to several clinical candidates of Factor Xa inhibitors and P2Y12 antagonists programs for the treatment of thrombosis. In 2013, he joined the Leibniz Institute for Molecular Pharmacology FMP to establish the medicinal chemistry group in the chemical biology department. His research interest is focused on the structure-based design and optimization of chemical probes and imaging tools for chemical biology.

# PROTEIN-LIGAND INTERACTIONS: HOW MEDICINAL CHEMISTRY CONTRIBUTES TO THE UNDERSTANDING OF MOLECULAR RECOGNITION

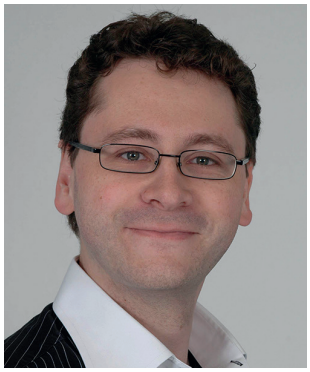
**Marc Nazaré**

*Leibniz-Forschungsinstitut für Molekulare Pharmakologie FMP, Campus Berlin-Buch, 13125 Berlin, Germany*

Multiple weak interactions govern the recognition of a small molecule to a protein binding site. Despite tremendous efforts to decipher how synergistic weak interactions impact a protein-ligand interface, it is still difficult to predict the binding affinity of a ligand to a protein target. During the process of a medicinal chemistry optimization in particular activity cliffs that are observed by subtle changes in the scaffold, a substituent or even in single-atom exchange, can be used in a the structure-based investigation to probe critical interactions.

A deeper insight and understanding of the interaction pattern was crucial for a structure-guided virtual deconstruction and hybridization approach using two privileged substructures. This gave instant access to a new series of highly selective tankyrase inhibitors by preserving key protein-ligand contacts. The high selectivity, favorable in-vitro ADME profile, and good oral bioavailability in mice, rats, and dogs makes these compounds a high quality chemical tools for proof of concept studies.

A single-atom substitution SAR approach was used to assess the strength of essential higher halogen π-aryl contacts in three congeneric series of fXa ligands. These data were supported by X-ray crystallography and computational methods. In addition, the design of torsional balances as unimolecular model systems was used to further dissect the energetics of this interaction. By these means, we found that higher halogen π-aryl interactions can be of similar strength to π-aryl cation interactions, which signifies additional versatility to structural design of ligands when considering lipophilic aromatic protein environments. Lessons learned from these fundamental studies are directly applicable to structure optimization in drug discovery research and extend the repertoire of rational approaches for ligand design.



# Prof. Edward TATE

IMPERIAL COLLEGE LONDON, LONDON, UNITED KINGDOM

Edward Tate is Professor of Chemical Biology in the Department of Chemistry at Imperial College London, and a Satellite Group Leader and the Francis Crick Institute. He completed his Ph.D. in organic chemistry at the University of Cambridge in the group of Prof. Steve Ley. Following postdoctoral research in chemistry and biology on an 1851 Research Fellowship at CNRS Gif sur Yvette and Ecole Polytechnique and the Pasteur Institute in Paris, he moved to Imperial College London on a BBSRC David Phillips Fellowship, where he was promoted to a Chair in 2014. He leads a team of more than 50 scientists working on the design and application of chemical approaches to understand and manipulate living systems, with a particular focus on drug target discovery and validation. He is a Fellow of the Royal Societies of Chemistry (FRSC) and of Biology (FRSB), and Director of Imperial's Centre for Drug Discovery Science. He received the 2012 Wain Medal, the 2013 MedImmune Protein and Peptide Science Award, the 2014 Norman Heatley Award, and a 2015 Cancer Research UK Programme Foundation Award in recognition of his group's research in chemical biology and drug discovery. Website: http://www.imperial.ac.uk/people/e.tate.

# ADVENTURES IN TARGETING PROTEIN LIPDATION: BREAKING DRUG RESISTANCE USING FRAGMENT DECONSTRUCTION AND CHEMICAL BIOLOGY

**Edward Tate**

*Imperial College London, Department of Chemistry, Chemical Biology Section, Exhibition Road, SW7 2AZ London, United Kingdom*

My group develops chemical biology approaches to identify and validate potential drug targets, particularly in the field of protein post-translational modification. In this talk I will discuss our recent work in the field of protein lipidation (acylation, cholesterylation and prenylation), where we have contributed to biological and pharmacological validation of protein targets in infectious diseases caused by parasites (e.g. malaria), bacteria and viruses, and in cancer. I will also illustrate how we have used chemical tagging technologies in an analytical platform for quantification and identification of protein lipidation in live cells and animals, providing the first insights into how lipidation changes in response to drug treatment at the whole proteome level. This research has enriched our understanding of these traditionally challenging classes of protein modification and delivered novel small molecules into pre-clinical development through fragment-guided drug discovery.

# Dr Goncalo BERNARDES

INSTITUTO DE MEDICINA MOLECULAR, PORTUGAL &
UNIVERSITY OF CAMBRIDGE, CAMBRIDGE, UNITED KINGDOM

After completing his D.Phil. degree in 2008 at the University of Oxford, U.K., he undertook postdoctoral work at the Max-Planck Institute of Colloids and Interfaces, Germany, and the ETH Zürich, Switzerland, and worked as a Group Leader at Alfama Lda in Portugal. He started his independent research career in 2013 at the University of Cambridge as a Royal Society University Research Fellow, and in 2018 he was appointed as a University Lecturer. His research group interests focus on the use of chemistry principles to tackle challenging biological problems for understanding and fight cancer.

# CHEMICAL PHYSIOLOGY OF ANTIBODY CONJUGATES AND NATURAL PRODUCTS

**Gonçalo Bernardes**

*Instituto de Medicina Molecular Lisbon & University of Cambridge*

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

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

(ii) bioorthogonal cleavage reactions for targeted drug activation in cells [2]

(iii) by identifying on- and off-targets for anti-cancer entities using our own machine intelligence platform, unveiling the underlying molecular mechanisms of target recognition and linking drug target binding to modulation of disease, we explore the use of natural products as selective cancer modulators [3]

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# Dr Mickael MOGEMARK

ASTRAZENECA, MÖLNDAL, SWEDEN

Mickael Mogemark is a medicinal chemist/ chemical toxicologist at AstraZeneca Gothenburg. He was awarded his Ph. D in chemistry from Umeå University, Sweden in January 2005. He joined AstraZeneca as a medicinal chemist in 2004 where he has worked across several therapy areas. His research interests are focused on chemical toxicology and on the development of novel therapeutic agents.

# SAFETY FIRST: COVALENT INHIBITORS FROM A SAFETY PERSPECTIVE

**Mickael Mogemark**

*AstraZeneca, RIA Medicinal chemistry, Pepparedsleden 1, 431 83 Mölndal, Sweden*

Many drugs which act via a covalent binding mode of action have found their way to the market to become life changing drugs and a few of them have been designated block buster status. Non-specific binding to other proteins has traditionally been cited as the main justifications to avoid the incorporation of reactive groups into new drug candidates due to risk of hepatoxicity (one of the main reason for preclinical compound attrition), immune-mediated toxicity and genotoxicity. Hence, covalent inhibitors have for many years been viewed as a liability, rather than an opportunity, due to fear of being subject to the same toxicity concerns as bioactivated reactive metabolites. However, a covalent approach is very appealing since it might increase both the specificity and efficacy which ultimately results in increased therapeutic margins and less-frequent drug dosing and for patients. This presentation highlights the importance of improving therapeutic index by adjusting specificity and examples where a targeted covalent inhibitor approach has been used to increase selectivity will be discussed.

# Prof. Christopher J. SCHOFIELD

UNIVERSITY OF OXFORD, OXFORD, UNITED KINGDOM

Chris Schofield studied for a degree in chemistry at the University of Manchester (1979-1982). In 1982 he moved to Oxford for DPhil studies with Jack Baldwin on the synthesis and biosynthesis of antibiotics. In 1985 he became a Departmental Demonstrator in the Dyson Perrins Laboratory, and in 1990 Lecturer in Chemistry and Fellow of Hertford College. In 1998 he became Professor of Chemistry, and in 2011 was appointed Head of Organic Chemistry. He is a Fellow of the Royal Society.

His research group works at the interface of chemistry, biology and medicine. His work has opened up new fields in antibiotic research, oxygen sensing and gene regulation in organisms ranging from bacteria to plants and animals. His work has identified new opportunities for medicinal intervention that are being pursued by numerous academic and commercial laboratories.

# ADVENTURES IN FUNCTIONAL ASSIGNMENT AND INHIBITION OF METALLO-ENZYMES

**Christopher Schofield**

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

Metallo enzymes play roles in the biosynthesis ($Fe^{II}$-oxygenases) of beta-lactam antibiotics and in resistance mechanisms to them ($Zn^{II}$-beta-lactamases). Human homologues of these bacterial enzymes have roles including in the regulation of protein biosynthesis and in nucleic acid damage repair. The lecture will describe work on the structures, mechanisms and biological roles of these two families of metallo-enzymes. It will then describe how their inhibition is being exploited in the development of new therapies for the treatment of diseases including anaemia and methods for combating antibacterial resistance.

## Dr Tjeerd BARF

ACERTA PHARMA BV, OSS, THE NETHERLANDS

Dr. Barf is one of the founders of Acerta Pharma. He has extensive experience in pharmaceutical Research and Development and contributed to delivery of several clinical candidates in the metabolic disease, autoimmune and oncology space. He successfully exploited the covalent binding paradigm for kinases, resulting in the discovery of acalabrutinib. Tjeerd joined the pharmaceutical industry in 1997 and served in various project and line management roles at Pharmacia & Upjohn, Biovitrum, Organon, Schering-Plough and MSD. He holds a PhD in Medicinal Chemistry and MSc in Organic Chemistry from the University of Groningen, The Netherlands.

# MINING THE PROTEIN KINASE CYSTEINOME

**Tjeerd Barf**

*Medicinal Chemistry, Acerta Pharma BV, Oss, The Netherlands*

In only a few decades, the human protein kinome has been successfully confirmed as a druggable target family. As much as 47 NME kinase inhibitors (and counting) have been approved since the first entry in 2001, and many more are being evaluated in clinical trials. More recently, the cysteines in the ATP binding pocket have been exploited with the aim to develop covalent kinase inhibitors, which allows for differentiating properties compared to conventional reversible binding modalities. This already led to market introductions of six irreversible covalent kinase inhibitors for oncology indications such as non-small cell lung cancer and B cell blood cancers. The breadth and scope of the general concept will be reviewed, featuring case studies of Acerta drug discovery projects concerning the kinases that play a pivotal role in cancer.

## Prof. Mark WALLER

UNIVERSITY OF WOLLONGONG, WOLLONGONG, AUSTRALIA

Dr. Mark P Waller is the founder of Pending.AI, a startup based in Sydney, Australia. The company is developing AI solutions to empower scientists in the pharmaceutical industry to design, make, and test new drugs to treat diseases. Mark was formerly at Shanghai University in Shanghai, China, where he was an Eastern Scholar Professor in the department of Physics. Prior to that he was in the Organic Chemistry Institute at University of Münster, Germany where he worked towards getting his Habilitation on adaptive multi-scale modeling. Mark first went to Germany over 12 years ago as a post-doc at the Max-Planck-Institut für Kohlenforschung where he worked on NMR. He obtained his PhD from the University of Sydney in Charge Density, and before that he carried out his undergraduate studies at the University of Tasmania where he obtained a Bachelor of Science.

# LEARNING THE ART OF CHEMICAL SYNTHESIS WITH DEEP NEURAL NETWORKS AND DISCIPLINE SCALE DATA

**Mark P. Waller**

*Pending.AI , iAccelerate, Innovation Campus, Squires Way, North Wollongong, NSW 2500, Australia, https://pending.ai*

Chemists have tried to algorithmically discover the rules of chemistry since E. J. Corey's seminal work in the 1960s. We have demonstrated how well modern methods could perform when planning complex retrosynthetic routes.[1] This accomplishment was built on top of two key technologies: firstly, we showed that single step reactions could be quickly predicted using a neural network.[2,3] Secondly, the other key component was an algorithm known as Monte Carlo Tree Search (MCTS). We trained our neural netoworks on the REAXYS database.[4] We validated our approach on 497 randomly selected targets, and performed double blind AB testing.

We have also developed a method to generate novel molecular targets using recurrent neural networks (RNN).[5] This enables us to quickly discover new areas of chemical space that might contain highly valuable compounds. However, the number of molecules that are produced by the RNN is immense, and the bottleneck becomes assessing their synthesizability. Therefore we can couple the two methods together by firstly generating new ideas (RNN), and then filter out coumpounds that have no known routes (MCTS).

We have also developed a novel method for reaction prediction and retrosynthesis based on link prediction.[6] This means we are not limited to rules based approaches, so we can effectively discover brand new reactions that have no precedence in the literature.

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## Dr Pat WALTERS

RELAY THERAPEUTICS, CAMBRIDGE, UNITED STATES

Pat Walters heads the Computation & Informatics group at Relay Therapeutics in Cambridge, MA. His group focuses on novel applications of computational methods that integrate computer simulations and experimental data to provide insights that drive drug discovery programs. Prior to joining Relay, he spent more than 20 years at Vertex Pharmaceuticals where he was Global Head of Modeling & Informatics. Pat is a member of the editorial advisory board for the Journal of Medicinal Chemistry, and previously held similar roles with Molecular Informatics, and Letters in Drug Design & Discovery. Pat received his Ph.D. in Organic Chemistry from the University of Arizona where he studied the application of artificial intelligence in conformational analysis. Prior to obtaining his Ph.D., he worked at Varian Instruments as both a chemist and a software developer. Pat received his B.S. in Chemistry from the University of California, Santa Barbara.

# APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY – SEPARATING HYPE FROM UTILITY

**Pat Walters**

*Relay Therapeutics, 215 First Street, MA 02142 Cambridge, United States*

Computational Chemistry has been a component of drug discovery efforts for more than 30 years. While the impact of computation has varied between organizations, its value is now widely, if not universally, acknowledged. Over the last 20 years, the role of the computational chemist has evolved from that of a craftsperson who individually tuned single molecules to the data wrangler who must identify trends in the multitude of biological assays that are run during the course of a drug discovery program. More recently, computational chemists have begun to embrace and employ techniques that have been developed as part of data science and machine learning efforts.

In essence, machine learning can be thought of as "using patterns in data to label things." In drug discovery, machine learning can take a number of different forms ranging from the classification of phenotypes from cellular images to models for predicting physical properties and biological activity. Much of the recent hype around AI has centered on the application of deep neural networks, often referred to as "deep learning". While many refer to neural networks as motivated by the human brain, they are really just systems for fitting non-linear relationships to data. While deep learning has revolutionized a number of areas including image recognition and language translation, its application to quantitative structure-activity relationships is still a work in progress.

One factor driving the rapid adoption of machine learning in drug discovery is the availability of software tools for building machine learning models. Software that was once only available to machine learning researchers is now freely available for download. Organizations such as Facebook, Google, and Amazon are now releasing Open Source software tools for machine learning that can be applied to problems in numerous domains including drug discovery. While these new tools offer an array of opportunities, we must be adequately prepared to use them effectively. Researchers need to have a sufficient command of the underlying science to develop representations that can be processed by machine learning algorithms. Scientists applying machine learning in drug discovery must have sufficient computational skills to be able to adopt and apply these techniques. Finally, researchers must have an understanding of statistics that will enable them to assess and improve the quality of their models.

Ultimately. the success of any predictive model comes down to three factors; data, representation, and algorithms. The data being generated must be relevant, and the experimental error must be well characterized. In order to build a predictive model, we must be able to create a representation of the data, typically as some sort of vector, that can be processed by a machine learning algorithm. The algorithm can then identify relationships between the data and some observable (e.g. biological activity) and can subsequently be used to make predictions on new data.

## NOTES

# ORAL COMMUNICATIONS – ABSTRACTS & BIOSKETCHES

## Dr Christian STEINEBACH

UNIVERSITY OF BONN, BONN, GERMANY

Christian Steinebach completed his undergraduate studies in Pharmacy (state examination) at the University of Bonn, Germany. In 2015, he became a licensed Pharmacist and got the Carl-Friedrich-Mohr award. He received his MSc in Drug Development in 2016. Since then he is performing his PhD studies in Pharmaceutical Chemistry supervised by Prof. Michael Gütschow at the Pharmaceutical Institute in Bonn. In 2018, he successfully applied for a PhD-related scholarship from the Bonn International Graduate School of Drug Sciences. His scientific work is devoted to the Medicinal Chemistry of Proteolysis Targeting Chimeras (PROTACs), to the design and synthesis of bioactive molecules acting by a new modality of targeted degradation of disease causing proteins, as well as to general questions about the utilization of the ubiquitin-proteasome system.

# SMALL-MOLECULE MODULATION OF CEREBLON PROTEIN LEVEL

**Christian Steinebach (1), Stefanie Lindner (2), Hannes Kehm (2), Lan Phuong Vu (1), Jan Krönke (2), Michael Gütschow (1)**

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*2) University Hospital Ulm, Department of Internal Medicine III, Albert-Einstein-Allee 23, D-89081 Ulm, Germany*

Small-molecule control of intracellular protein levels could provide both novel therapeutics and tools for the study of biological systems. The ability of a small molecule to target a protein for degradation is an exciting implication for modern drug discovery. One such approach is based on the chemical-induced degradation of disease-causing proteins by heterobifunctional molecules, referred to as Proteolysis Targeting Chimeras (PROTACs) which induce ubiquitination and targeted proteasomal degradation.[1)]

Cereblon (CRBN) is a multifunctional protein that is involved in different cellular processes and diseases. For example, a CRBN mutation is associated with human autosomal recessive nonsyndromic mental retardation. Genetic inactivation of CRBN confers resistance to sepsis and prevents high-fat-diet induced obesity and insulin resistance in mice, implying that pharmacological inhibition of CRBN may have clinical applications. The multiprotein structure of E3 ligases and the lack of pharmaceutically targetable regions on the protein surface have so far impeded the generation of specific inhibitors for these enzymatic complexes. CRBN has drawn attention as the target of the immunomodulatory imide drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide that are mainstays in the treatment of multiple myeloma. These drugs mediate their activity in cancer by modulating the specificity of the $CRL4^{CRBN}$ E3 ligase to degrade so-called neo-substrates.[2,3)] Genetic inactivation of CRBN has been shown to cause resistance to IMiDs in cell lines, and inactivating CRBN mutations were detected in IMiD-resistant multiple myeloma patients.

We sought for a chemical knockdown of the E3 ligase cereblon (CRBN), to attain deeper knowledge of its multiple functions. For this purpose, we designed and synthesized small-molecules which are capable of inducing the degradation of cereblon.[4,5)] A summary of our chemical attempts to modulate the protein homeostasis of CRBN in unmodified systems will be presented, including hydrophobic tagging and PROTAC molecules. The latter were found to be highly effective to control CRBN protein levels *via* the ubiquitin-proteasome system at nanomolar concentrations.

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## Ms Míriam MARTÍNEZ-CARTRÓ

UNIVERSITY OF BARCELONA, BARCELONA, SPAIN


Míriam Martínez-Cartró obtained her bachelor's degree in Pharmacy at the University of Barcelona. She is currently a PhD student under the supervision of Prof. Xavier Barril and Dr. Carles Galdeano at the Faculty of Pharmacy of the University of Barcelona. Her PhD project is focused on the identification and characterization of chemical probes able to bind relevant SCF-E3 ligase through the application of a multidisciplinary approach that combines structure-based drug design and biophysical techniques for hit identification.

During her PhD she carried out a placement in the Structural Genomics Consortium of Oxford under the supervision of Prof. Frank von Delft to perform X-Ray crystallography of small-molecules for therapeutic interest.

# DRUGGING CHALLENGING E3 LIGASES: A NOVEL MULTIDISCIPLINARY APPROACH TO IDENTIFY SMALL-MOLECULES THAT BIND FBW7

**Míriam Martínez-Cartró (1), Salvatore Scaffidi (1), Xavier Barril (1,2), Carles Galdeano (1)**

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During normal cellular homeostasis, proteins are constantly synthesized and destroyed. The most common degradation pathway for proteins is the Ubiquitin Proteasome System (UPS), a highly regulated signalling cascade that is ultimately responsible for the controlled degradation of a large number of proteins. E3 ligases provide substrate specificity to this system, making them extremely attractive candidates as drug targets. However, the development of small-molecules against E3 ligases has led to limited success, in part because modulating their activity and regulation requires targeting protein-protein interactions.[1]

Fbw7 is an important E3 ligase and one of the most commonly deregulated proteins in human cancers. Indeed, 6% of cancers have mutations in the *fbw7* gene. On one hand, the loss of activity of the mutated Fbw7 results in a loss of its tumour suppressor function and an upregulation of the natural and oncogenic substrate proteins: c-Myc, cyclin-E, Notch, etc.[2] On the other hand, the inhibition of Fbw7 has been proposed as an approach to sensitize cancer stem cells to chemotherapies.[3] However, so far, no potent small-molecules directly targeting Fbw7 have been reported. In this project, using a novel multidisciplinary approach, we aim to identify small-molecules that targets Fbw7 to disentangle the more convenient pharmacological strategy to manipulate it. Moreover, targeting this E3 ligase would not only be significant for its pharmacological relevance, but also for the development of PROteolysis TArgeting Chimera moleculeS (PROTACS).

To identify *ligandable* allosteric sites in the Fbw7-Skp1 surface we have applied MDmix simulations.[4] Docking-based virtual screening applying Duck[5] filter has been performed to find potential *hits*. These potential *hits* have been tested by Surface Plasmon Resonance and confirmed by STD-NMR. Following this workflow, we have been able to identify molecules that target Fbw7 in the one digit micromolar range. In parallel, a fragment-based screening has been performed and several fragments have also been identified. Work is on-going to obtain structural information that will confirm us the binding site and binding mode of these *hits*.

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# Dr Charlotte GRIFFITHS-JONES

ASTEX PHARMACEUTICALS, CAMBRIDGE, UNITED KINGDOM

Charlotte Griffiths-Jones gained a PhD from Cardiff University in 2004 then undertook a post doc in Cambridge under the supervision of prof Steve Ley. After 1 year at GSK working in the technology development lab, she moved to Astex in 2007 where she is now an Associate Director. Charlotte has worked on a number of fragment based drug discovery projects from early stage right through to clinical development. This includes the recently launched oncology drug Erdafitinib.

# CHEMICAL BIOLOGY FOR DRUG DISCOVERY: A CLICK AND PLAY APPROACH EXEMPLIFIED BY ERK1/2 PROBES

**Charlotte Griffiths-Jones**

*Astex Therapeutics, 436 Cambridge Science Park, Cambridge, CB4 0QA, UK*

The RAS-RAF-MEK-ERK signalling cascade is activated through mutations in RAS or RAF in over 30% of cancers. The successful development of inhibitors of BRAF and MEK kinases has led to effective treatment, particularly of melanomas whose tumour growth is driven by activating mutations in BRAF such as V600E. Despite these successes, resistance often emerges after several months. ERK1/2 inhibitors are therefore of key interest as an alternative approach to block this pathway, and several are already in early clinical trials.

Some inhibitors have been shown to reduce the phosphorylation of ERK itself in addition to inhibiting the phosphorylation of downstream substrates such as RSK. We sought to understand the structural link to this pharmacological effect by using X-ray crystallographic fragment screening to develop a series of orally bioavailable ERK inhibitors. The lead compound[1] shows low nanomolar potency in biochemical ERK1/2 assays and an excellent kinome selectivity profile.

In order to increase our understanding of ERK1/2 pharmacology, we developed trans-cyclooctene tagged clickable probes based upon published ERK inhibitors. We have used these probes in a range of chemical biology experiments.

Using the inverse electron demand Diels-Alder (IEDDA) cycloaddition, we have applied the 'click and play' concept to our ERK1/2 probes. By clicking our probe with a fluorescent dye tagged with a tetrazine (Tz) group, its selectivity profile[2] and cellular localisation[3] were studied via in-gel fluorescence and fluorescence imaging, respectively. We demonstrated that ERK1/2 proteasomal degradation was induced in-cell through the reaction of Probe 1 with Tz-thalidomide, a ligand of the E3 ligase cereblon.[4] Other chemical biology experiments can be conducted via the 'click and play' approach and these will be discussed.[5]

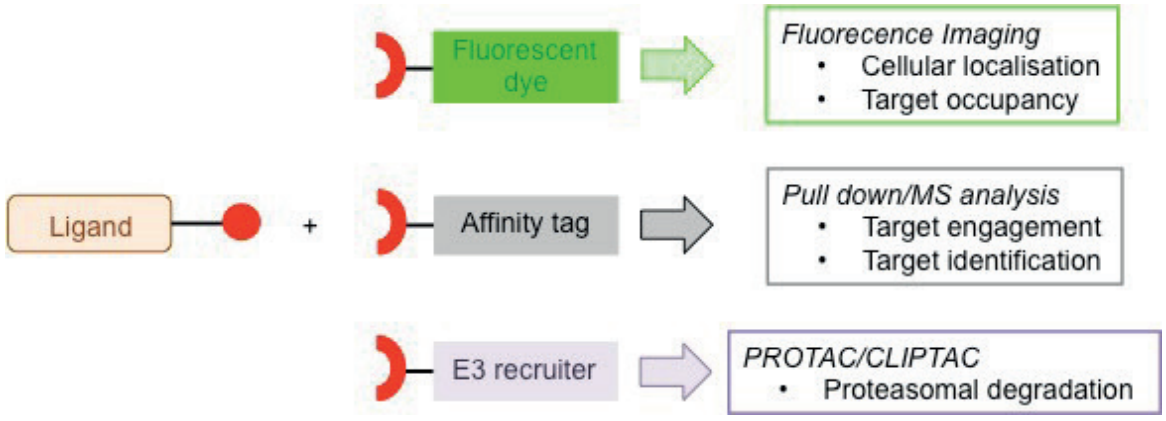


Figure 1: The 'click and play' approach

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# Dr Sven RUF

SANOFI-AVENTIS DEUTSCHLAND GMBH,
FRANKFURT AM MAIN, GERMANY

Dr Sven Ruf completed his PhD studies in synthetic organic chemistry with Prof. Regitz at the University of Kaiserslautern in 1999. Afterwards he spent the year 2000 with postdoctoral studies in the group of Prof. Trost at Stanford University.

In 2001 he joined the medicinal chemistry department of the Sanofi-Aventis Deutschland GmbH and currently holds the position of a senior scientist. He has been responsible for the lead discovery strategies deployed in several early resarch projects and is a team and project leader at the Sanofi research site in Frankfurt.

# IDENTIFICATION AND IN-VIVO EFFICACY STUDIES OF A NICOTINAMIDE DERIVATIVE AS NOVEL NNMT INHIBITOR

**Sven Ruf (1), Mahanandeesha Siddappa Hallur (2), Nisha K. Anchan (2), (2), Indu N. Swamy (2), Karthikai Raj Murugesan (2), Sayantani Sarkar (2), Lokesh Kananti Narasimhulu (2), V.P. Rama (2), Kishore Putta (2), Shama Shaik (2), Devaraj Venkatapura Chandrasekar (2), Vishal Subhash Mane (2), Sanjay Venkatachalapathi Kadnur (2), Juluri Suresh (2), Ravi Kanth Bhamidipati (2), Manvi Singh (2), Raghunadha Reddy Burri (2), Rajendra Kristam (2), Herman Schreuder (1), Joerg Czech (1), Christine Rudolph (1), Alexander Marker (1), Thomas Langer (1), Ramesh Mullangi (2), Takeshi Yura (2), Ramachandraiah Gosu (2), Aimo Kannt (1,3), Saravanakumar Dhakshinamoorthy (2), Sridharan Rajagopal (2)**

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*2) Jubilant Biosys Ltd. Bangalore, 560022 India*
*3) Institute of Experimental Pharmacology, Medical Faculty Mannheim, University of Heidelberg, D-68167 Mannheim, Germany*

Obesity is considered as one of the major risk factors of development of insulin resistence and Type 2 diabetes (T2D). Nicotinamide N-methyl transferase (NNMT), an enzyme that catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to nicotinamide (NA) to form N-methylnicotinamide (MNA) is implicated in the regulation of body weight and insulin sensitivity.

NNMT is expressed in the liver, adipose and other tissues.[1,2] Several reports have suggested the role of NNMT in various disease conditions including metabolic disorders.[3-5] Increased expression of NNMT has also been linked to enhanced cell proliferation and disease progression in a wide variety of cancers. It is also known that NNMT is up-regulated in Parkinsons's disease and in ageing skeletal muscle tissue. [6-8] Recent reports have highlighted the relationship between high expression of NNMT and obesity/T2D [9,10]. In our work we identified a novel nicotinamide (NA) derivative, that was able to inhibit the NNMT enzymatic activity in vitro and reduced the in-vivo formation of 1-methyl-nicotinamide (MNA), the primary metabolite of NA by ~80% after 2 h when administered to mice at 50mg/kg p.o.

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# Dr Dominique SURLERAUX

BCI PHARMA, LIÈGE, BELGIUM

Dominique Surleraux is Chief Executive officer (CEO) of BCI Pharma.

BCI Pharma was founded in March 2013 and is actually located in France (Montpellier) and Belgium (Liège).

Dominique Surleraux has a Ph.D in organic chemistry from university of Namur (BE) and a master in drug design (Lille, FR).

Dr. Dominique Surleraux started his career at Janssen Phamaceutica (J&J (BE), 5 years), then moved to Tibotec (J&J (BE), 7 years) and was managing worldwide anti-infective research for J&J.

He then moved to France and supervised the HCV research (60 scientists) for idenix Pharmaceutical, a Boston based company acquired by MSD (4b$).

He was directly involved on the discovery of blockbusters (Prezista (HIV protease Inh.) and Simeprevir (HCV protease Inh.) and bring more than 10 drugs in clinical development.

He is inventor/co-inventor of more than 100 patents.

# DISCOVERY OF BEST IN-CLASS, NOVEL, SELECTIVE, POTENT AND PERIPHERAL FLT3 INHIBITORS, A NEW WAY TO TREAT NEUROPATHIC PAIN

**Dominique SURLERAUX**

*BCI Pharma, Medicinal Chemistry Department, Liège, Belgium*

Few years ago, there was a need for a new type of molecule/scaffold as kinase inhibitor.

In 2013, BCI Pharma initiated a molecular modeling project, design a proprietary chemical library and synthese the most promising inhibitors (500) based on docking results.

Final compounds were evaluated in target based assay (subset of 40 kinases) and among hits, FLT3 inhibitors has been identified.

These hits were further optimized and very selective and potent lead compounds have been profiled in in-vitro assay (cell-based, Caco-2, microsome, hepatocyte, protein binding), in-vivo DMPK studies (mice, rat, dog) and later efficacy data for 10 compounds have been generated in different neuropathic pain and pain/inflammation animal models.

The lead optimisation and animal efficacy will be presented.

# Prof. James BREITENBUCHER

UNIVERSITY OF CALIFORNIA SAN FRANCISCO,
SAN FRANCISCO, UNITED STATES

Dr. Breitenbucher has over 20 years of drug discovery experience and is currently Professor at the Institute for Neurodegenerative Diseases at UCSF.

Prior to joining UCSF, Dr. Breitenbucher was senior director of Chemistry at Dart Neurosciences. During his 8 years at DNS he built a robust department that discovered 10 novel pre-clinical candidates for 7 different biological mechanisms for the treatment of Stroke, Alzheimer's, and Parkinson's Disease.

Prior to DNS Guy was a research fellow at Johnson & Johnson as head of the Pain Discovery Chemistry. At J&J, Dr. Breitenbucher worked on or led drug discovery projects on 10 different biological mechanisms which advanced compounds into pre-clinical or clinical development. Dr. Breitenbucher received his B.Sc. and M.Sc. in chemistry at California State University at Long Beach and his Ph.D. in organic chemistry at University of California at Riverside. Dr. Breitenbucher is co-author on over 50 peer reviewed scientific papers, an inventor on over 40 patents.

# THE DISCOVERY AND DEVELOPMENT OF THE CLINICAL FAAH INHIBITOR JNJ-42165279

**James Breitenbucher (1), Sandra Chaplan (2), John Keith (2), James Palmer (2), Mark Tichenor (2), Mark Seierstad (2), Michele Rizzolio (2), Sandy Wilson (2)**

*1) UCSF, Sandler Neuroscience Center, San Francisco, CA 94158, United States*
*2) Janssen Research Labs, San Diego, CA 92121, United States*

Inhibition of fatty acid amide hydrolase (FAAH) potentiates endocannabinoid activity and is hypothesized to have therapeutic potential for mood and anxiety disorders and pain. We will present the story of the discovery and development of the current Janssen clinical candidate JNJ-42165279, which is undergoing Phase II clinical trials for the treatment of anxiety disorders. The Medicinal chemistry discovery will be presented along with discussion of the development of a covalent FAAH drug in the context of safety and PK/PD. We will present pre-clinical PK/PD data as well as clinical PK, pharmacodynamics, safety, and binding to FAAH in the brain of healthy human volunteers.

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## Dr Agnieszka BARTOSZEWICZ

ONCOARENDI THERAPEUTICS SA, WARSZAWA, POLAND

Agnieszka completed her PhD studies in organic chemistry under the supervision of Prof. Belén Martín-Matute at Stockholm University, Sweden in 2012. Afterwards she spent 2 years as a postdoctoral fellow in the group of Prof. Gregory Fu at Caltech, Pasadena, CA, USA. She joined Oncoarendi Therapeutics SA in 2015 as a medicinal chemist. Agnieszka is currently a team and project leader at Oncoarendi working on design and synthesis of small molecule inhibitors targeting chitinase-like-proteins.

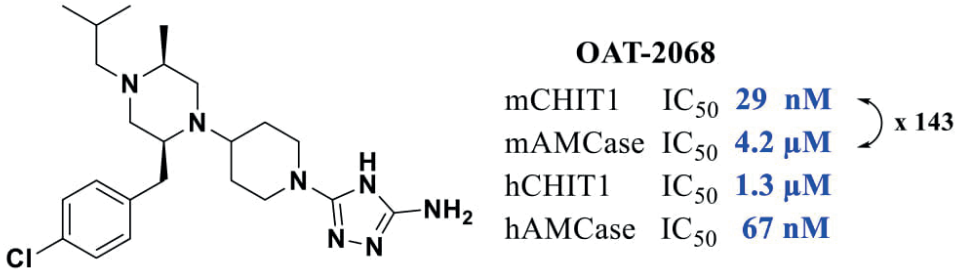
# DISCOVERY OF OAT-2068 - A POTENT, SELECTIVE, ORALLY BIOAVAILABLE INHIBITOR OF MOUSE CHITOTRIOSIDASE AND ITS IN VIVO ACTIVITY IN THE BLEOMYCIN-INDUCED PULMONARY FIBROSIS MODEL IN MICE

**Wojciech Czestkowski (1), Łukasz Joachimiak (1), Marzena Mazur (1), Sylwia Olejniczak (1), Robert Koralewski (1), Michał Kowalski (1), Barbara Dymek (1), Piotr Sklepkiewicz (1), Michał Mlącki (1), Gleb Andryianau (1), Elżbieta Pluta (1), Piotr Niedziejko (1), Krzysztof Matyszewski (1), Agnieszka Bartoszewicz (1), Mariusz M. Gruza (1), Agniesza Zagożdżon (1), Magdalena Salamon (1), Jakub Golab (2), Karolina Dzwonek (1), Paweł Dobrzański (1), Jacek Olczak (1), Adam Golebiowski (1)**

*1) OncoArendi Therapeutics SA, Żwirki i Wigury 101, 02-089 Warsaw, Poland*
*2) Department of Immunology, Medical University of Warsaw, Nielubowicza 5, 02-097 Warsaw, Poland*

Chitotriosidase (CHIT1) is a member of the chitinase family of hydrolases responsible for cleaving glycosidic bonds of chitin in mammals. It has been shown to be involved in various lung pathologies such as idiopathic pulmonary fibrosis, sarcoidosis, chronic obstructive pulmonary disease and asthma.

Herein, we report our work towards the identification of a potent and selective inhibitor of mouse chitotriosidase (mCHIT1). A series of small molecule inhibitors of mCHIT1 have been designed, synthetized, and evaluated in a panel of *in vitro* assays. Among them the lead compound **OAT-2068** displays a nanomolar activity towards mCHIT1, a remarkable 143-fold selectivity over the other chitinase mAMCase and has an excellent pharmacokinetic profile in mice. In addition to this excellent characteristics, anti-fibrotic *in vivo* efficacy of **OAT-2068** in the bleomycin-induced pulmonary fibrosis mouse model will be reported.



# Dr Anna KARAWAJCZYK

SELVITA, KRAKOW, POLAND

Dr Anna Karawajczyk joined Selvita as a team leader of computational chemistry in October, 2017. Prior to it she worked in various settings ranging from small biotech companies (LeadPharma, NL; Taros Chemicals, DE), big pharmaceutical industry (Organon/Schering Plough, NL) and in academia (CMBI, Radboud Univ, NL). While providing computational chemistry support she used to work in teams with medicinal/synthetic chemists and biologists. However, her Europe-wide recognition comes from her involvement in the European Lead Factory. She was responsible for the design and evaluation of novel scaffold proposals, comparative analysis of newly synthesized libraries (Drug Discovery Today 2015, 20, 1310–1316), as well as planning the synthesis and performing the enumeration of the libraries considering the lead-like properties of new compounds. Her experience as a computational chemist is complemented by her broad medicinal chemistry knowledge acquired during many successful hit ID and hit to lead campaigns.

# DPD-INSPIRED SMALL HETEROCYCLIC LIBRARIES CHARACTERIZED AS NOVEL LsrK KINASE INHIBITORS: AN OPPORTUNITY TO FIGHT ANTIMICROBIAL RESISTANCE

**Silvia Stotani (1,3), Viviana Gatta (2), Päivi Tammela (2), Simona Collina (3), Anna Karawajczyk (4), Fabrizio Giordanetto (1)**

*1) Medicinal Chemistry, Taros Chemicals GmbH & Co. KG, Emil-Figge-Straße 76a, 44227 Dortmund, Germany*
*2) Drug Research Program, Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, FI-00014 Helsinki, Finland*
*3) Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Viale Taramelli 12, 27100, Pavia, Italy*
*4) Selvita S.A., Park Life Science, Bobrzynskiego 14, 30-348 Krakow, Poland*

INTEGRATE project under the Marie Sklodowska Curie grant agreement N°. 642620

Resistance to antibiotics is constantly increasing and it is estimated that, by 2050, multidrug resistant bacteria will kill more people than cancer. In the last decade, modulation of QS has become an attractive therapeutic strategy to fight bacterial resistance. Two different DPD related compounds (i.e., isobutyl-DPD and phenyl-DPD) have already shown their activity in combination with gentamicin and small molecules able to modulate/inhibit QS are therefore considered interesting “non-conventional” tools to be used in combination with classical antibiotics. In this study, we report on the design, synthesis and SAR of novel DPD-related compounds with different core structures, involving modifications at the DPD diketo moiety. In particular, we explored five small libraries of DPD-inspired heterocyclic derivatives. Lastly, the in vitro inhibitory effect of the new compounds against LsrK has been evaluated. Results obtained suggested that Het-DPD derivatives act as LsrK inhibitors and their analogs may be considered as useful templates for the discovery of new effective DPD-based antimicrobial agents. To the best of our knowledge, these are the first heterocyclic-based LsrK inhibitors reported to-date.

## Dr Michal WARCHOL

ARDIGEN, KRAKOW, POLAND

Dr. Michał Warchoł serves as a Director of Ardigen AI Labs, leading the development and applications of statistical learning methods in Ardigen's projects. He did a PhD in Statistics at the Institute of Statistics, Biostatistics and Actuarial Sciences at Université Catholique de Louvain in Belgium. Part of his research program was conducted at the Department of Statistics at Columbia University in New York. Prior to joining Ardigen, Dr. Warchoł co-founded DeepArt UG, company providing novel image processing algorithms based on deep learning. He obtained a master degree in mathematics at the Jagiellonian University and a bachelor degree in finance at the Cracow University of Economics in Poland. The last year of his master program was done at the Department of Statistics at École polytechnique fédérale de Lausanne in Switzerland.

# AUGMENTED INTELLIGENCE FOR COMPOUND DESIGN

**Michał Warchoł**

*Ardigen S.A., Bobrzyńskiego 14, 30-348 Krakow, Poland*

Rapid development in artificial intelligence (AI) is one of the driving components of the fourth industrial revolution. Pharmaceutical and Healthcare industry is already taking advantage of the state-of-the-art machine learning algorithms providing e.g. more precise and cheaper diagnostics. In this talk I will show how most recent advancements in machine learning are applied in drug discovery process, in particular in the compound design phase.

# Mr Nick FOSTER

OPTIBRIUM, CAMBRIDGE, UNITED KINGDOM

**Nick Foster**
**Head of Commercial Operations**
**Optibrium**

Nick graduated with a degree in Applied Biochemistry in 1993 before joining the Medical Research Council working on protein folding within Cambridge University's Chemistry Department and the Laboratory for Molecular Biology (LMB) until 2001. After this, Nick helped establish the ADME/PK laboratory of Camitro and remained part of the operational team (within BioFocus) until 2009 when he joined the sales and marketing team as Associate Director of Business Development, Europe.

Nick joined Optibrium as Head of Commercial Operations in 2012. The company develops pioneering software for small molecule design, optimisation and data analysis.

# CAPTURING AND APPLYING KNOWLEDGE TO GUIDE COMPOUND OPTIMISATION

**Matthew Segall, Edmund Champness, Peter Hunt, Tamsin Mansley**

*Optibrium Ltd., F5-6 Blenheim House, Cambridge Innovation Park, Denny End Road Cambridge, CB25 9PB, UK*

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 [1]; MPO methods capture the desired property criteria for a successful compound for a specific project and rigorously prioritise ideas for consideration [2]; and, optimisation strategies can be captured as structural transformations that reflect steps made in previous chemistry projects [3,4].

We 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 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.

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## NOTES

# POSTER ABSTRACTS

# CUBANES FOR DRUG DESIGN

**I. Kos, O. Gaidai, R. Iminov, A. Tverdokhlebov, P. Mykhailiuk, A. Tolmachev**

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In 2016, chemists showed that replacing a benzene ring in the neurotropic compound *Leteprinim* with a skeleton of cubane beneficially affected activity and water solubility of the parent compound (Figure 1).[1] Since then the cubane-containing building blocks are gaining high popularity in drug discovery projects, as mimics for the benzene ring.[2-4]

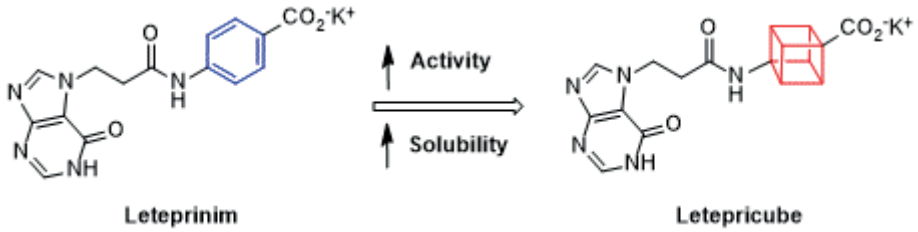
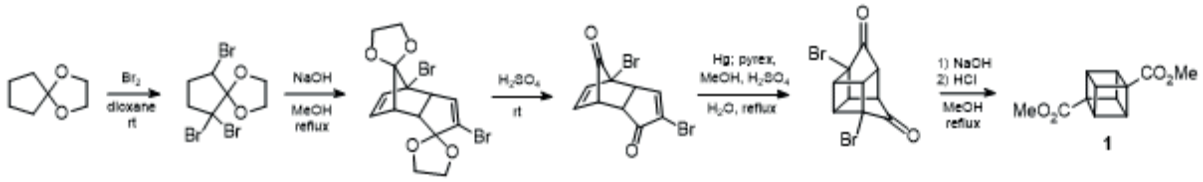
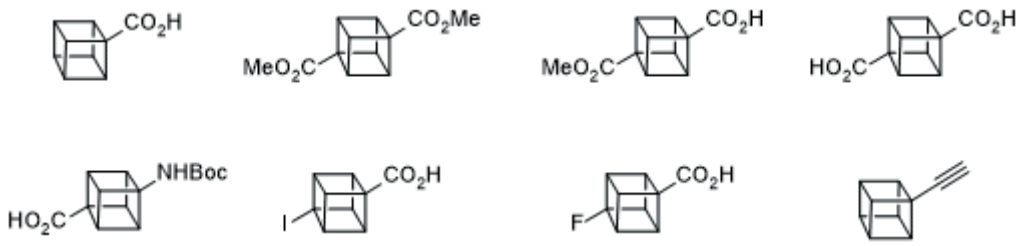



**Figure 1.** Modification and improvement of activity of Leteprinim drug.

We synthesized cubane-1,4-diester **1** in 100 g scale following the literature protocol (Schemes 1),[4] and used it for the synthesis of diverse cubane-containing building blocks (Schemes 2).




**Scheme 1.** Literature synthesis of cubane-containing compound **1**.[4]



**Scheme 2.** A library of cubane-containing building blocks for drug discovery programs.

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# NEW HYBRID DERIVATIVES OF 2-(2,5-DIOXOPYRROLIDIN-1-YL)-2-PHENYLACETAMIDE WITH ANTICONVULSANT AND ANTINOCICEPTIVE PROPERTIES IN THE PRECLINICAL STUDIES

**Michał Abram (1), Marcin Jakubiec (1), Anna Rapacz (2), Szczepan Mogilski (2), Gniewomir Latacz (3), Krzysztof Kamiński (1)**

*1) Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland*
*2) Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland*
*3) Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków,Poland*

In recently years the molecular hybridization has become the important method in the new drugs development especially in relation to diseases with complex pathomechanism, such as Alzheimer's disease, Parkinson's disease, cancer or epilepsy. This strategy assumes that a single chemical entity is capable of modulating biological targets simultaneously and overcoming problems related to the use of "multicomponent drugs" such as different bioavailabilities or pharmacokinetics, as well as poor compliance in case of "drug cocktails." According to this approach, two (or more) different molecules, each with the different target or with specific biological properties, are combined in a single chemical entity to provide broad activity.[1] Linking of different molecular mechanisms may be especially beneficial in the treatment of disease with the high-risk of drug resistance development, such as epilepsy. It should be emphasized that in the case of the aforementioned disease, in nearly 30% of patients pharmacotherapy does not produce expected improvement.[2]

Bearing in mind the assumptions of multi-target strategy and with the aim of obtaining new highly effective and broad-spectrum anticonvulsants, we have developed integrated hybrid molecules derived from the pyrrolidine-2,5-dione ring. These compounds overlap on the common structural framework the chemical fragments of three chemically and pharmacologically diversified ADEs such as ethosuximide, levetiracetam, and lacosamide. As a result, the hybridization process yielded substances with a potent and broad-spectrum anticonvulsant activity that joined pharmacological properties of all AEDs creating hybrid structures.[3-4]

Continuing research in the group of hybrid compounds derived from pyrrolidine-2,5-dione, and in the aim of obtaining compounds with more potent protection in the maximal electroshock (MES) test, the pentylenetetrazole-induced seizure model (PTZ), and the psychomotor 6 Hz (32 mA and 44 mA) seizure model in mice, in current studies we have obtained a new series of (2,5-dioxopyrrolidin-1-yl)(phenyl)acetamides. These hybrids demonstrated a wide spectrum of activity in the preclinical studies as they were effective in the most widely employed animal seizure models (MES, PTZ and 6 Hz (32 mA and 44 mA)). The most active was compound **(*R*)-KA-104**, ($ED_{50}$ MES = 36.0 mg/kg, $ED_{50}$ 6 Hz (32 mA) = 39.2 mg/kg; $ED_{50}$ PTZ = 54.8 mg/kg). In addition, this substance was effective in the 6 Hz (44 mA) model of drug resistant epilepsy ($ED_{50}$ = 117.0 mg/kg) and revealed high safety profile in the rotarod test ($TD_{50}$ = 468.5 mg/kg). Notably, compound **(*R*)-KA-104** demonstrated potent effectiveness by decreasing pain responses in formalin-induced tonic pain and in the streptozocin and oxaliplatin-induced neuropathic pain models in mice.

**The studies were supported by the Polish National Science Centre grant 2015/18/E/NZ7/00509.**

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# MULTITARGET DIRECTED LIGANDS TO TREAT ALZHEIMER'S DISEASE: NRF2 INDUCERS, CHOLINERGIC NEUROTRANSMISSION MODULATORS AND FREE RADICAL SCAVENGERS

**Sheila Abril (1,2), Izaskun Buendia (2), Patrycja Michalska (1,2), Jose Carlos Menendez (3), Irena Loryan (4), Margareta Hammarlund-Udenaes (4), Mercedes Salaices-Sanchez (1), Rafael Leon (2)**

*1) Instituto Teófilo Hernando y Departamento de Farmacología y Terapéutica, Facultad de Medicina, Universidad Autónoma de Madrid, 28029 Madrid*
*2) Instituto de Investigación Sanitaria del Hospital Universitario de la Princesa, 28006, Madrid*
*3) Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense de Madrid, 28040, Madrid*
*4) Department of Pharmaceutical Biosciences, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden*

Alzheimer's Disease (AD) is the most common form of dementia worldwide. Because of its great biological complexity, AD is considered a multifactorial disorder. Currently, there are only five FDA marketed symptomatic drugs, which cannot stop the disease progression [1]. This had led to develop the new therapeutic strategy of multitarget directed ligands (MTDL) [2].

In this context, we have obtained a new chiral MTDL family based on most important pathological routes involved in AD. Some of the fifteen *de novo* synthetized compounds were simultaneously free radical scavengers, Nrf2 transcription factor inducers, AChE inhibitors, nAChRs modulators and neuroprotectant agents.

The promising compounds were further studied to obtain pharmacokinetic (PK) and central nervous system distribution parameters following the "Combinatory Mapping Approach" [3]. The selected compounds showed a similar PK profile, with high both volumes of distribution and clearances. The NeuroPK studies revealed they distribute and bind to brain parenchyma, accumulating intracellularly. However, free unbound drug is low because of the existence an active efflux transport across blood brain barrier. This results are valuable to re-design a new family of multitarget directed ligands with advantageous physico-chemical properties to be able to cross BBB and distribute into the brain to exert their pharmacological response.

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# NEW POTENTIAL ANTIMYCOBACTERIAL AGENTS BASED ON 5-ALKYLAMINO-N-PHENYLPYRAZINE-2-CARBOXAMIDES

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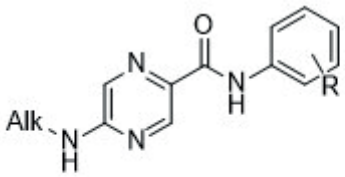
5-Chloropyrazinamide acts as an inhibitor of mycobacterial fatty acid synthase I (FAS I)[1]. With an appropriate substitution of this compound it is possible to increase antimycobacterial activity and reduce cytotoxicity of this moiety[1,2]. The series of compounds derived from the 5-chloropyrazinamide skeleton was obtained. As modifications were selected moieties such as a phenyl ring substituted with various function groups in amide position and alkylamines attached to pyrazine ring. 5-alkylamino-N-phenylpyrazine-2-carboxamides (Fig. 1) have been tested for activity against *Mycobacterium tuberculosis* H37Rv, *M. kansasii, M. avium, M. smegmatis* and *M. aurum*. Detailed description of obtained results will be presented on the poster.




Alk: propyl, butyl, pentyl, hexyl, heptyl, octyl
R: -Cl, -OH, -CF3, methyl, ethyl

**Fig. 1: 5-alkylamino-N-phenylpyrazine-2-carboxamide**

*This work was supported by the project EFSA-CDN (No.CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by ERDF.*

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# P(O)ME2-CONTAINING BUILDING BLOCKS FOR DRUG DESIGN

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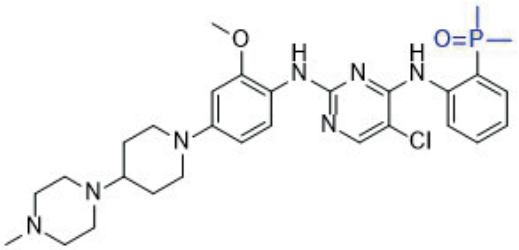
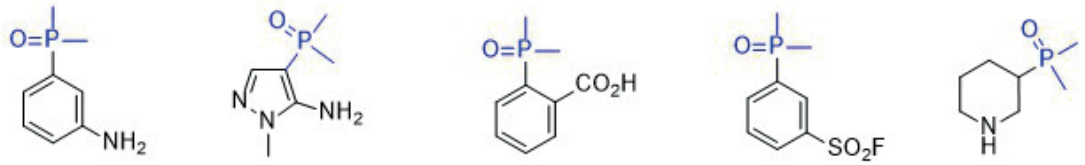
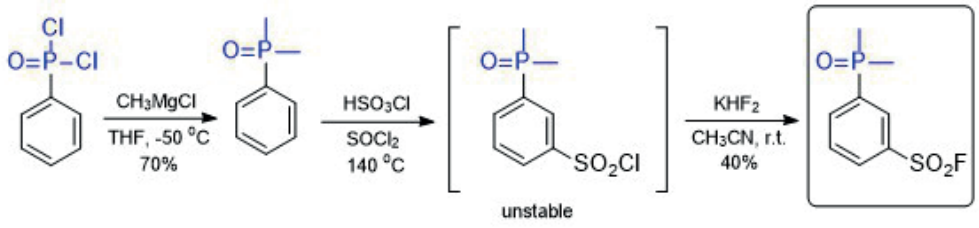
Phosphine oxides belong to a chemical class seldom employed in drug design. However, the FDA-approval of *Brigatinib* drug (ARIAD Pharm.) in 2017 may further inspire application of this unique functional group in medicinal chemistry. The highly ionic P=O bond imparts a number of important drug-like properties, including decreased lipophilicity, increased aqueous solubility, H-bond acceptor ability, and high metabolic stability.Herein we have designed and synthesized a library of phosphine oxide derivatives for drug design.



Anti-cancer drug **Brigatinib** (Alunbrig)
*ARIAD Pharm.*
2017







# CHEMICAL BIOLOGY OF EPIGENETIC NUCLEOSIDE ANALOGUES

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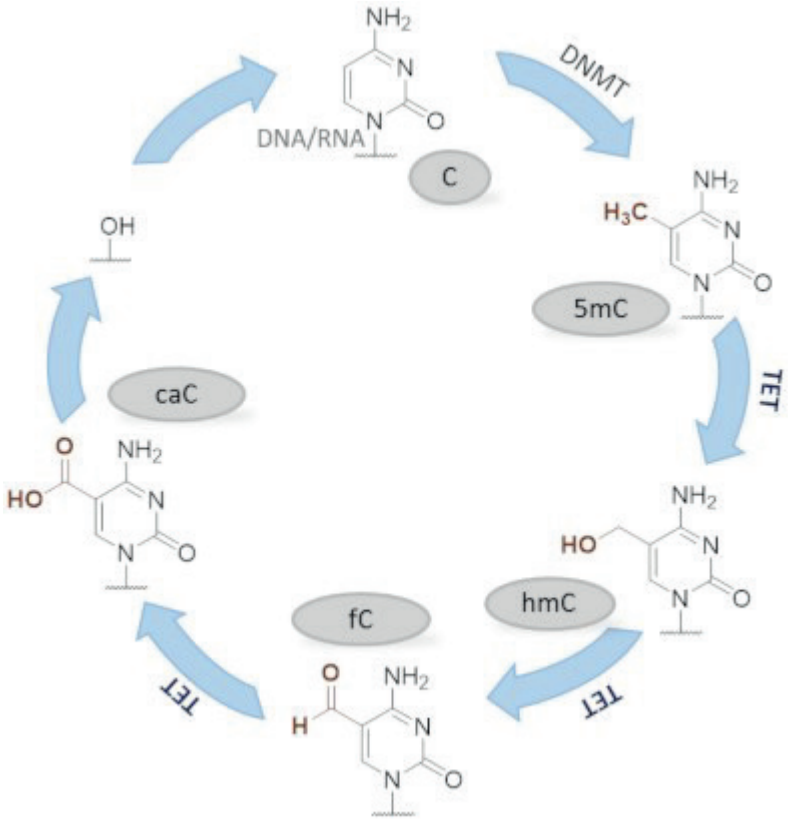
*2) Center for Biological Sciences, University of Nottingham, U.K.*

The epigenetic regulation of gene expression involves modifications to histones, DNA and RNA. These modifications include the novel bases m6A (6-methyladenosine) and hmC (5-hydroxymethylcytidine) in mRNA and DNA.[1] The family of TET (ten eleven translocation) enzymes catalyze the stepwise oxidation of 5mC (5-methylcytosine) to hmC and its further oxidation products, thereby leading to DNA demethylation. These enzymes are Fe(II) and 2OG (2-oxoglutarate) dependent.[2,3] As important regulators of DNA methylation level, TET enzymes play a critical role in tumor suppression and thus represent an interesting pharmaceutical target.




A significant limitation in understanding the role of epigenetic nucleotide modifications is the lack of suitable enzymatic assays. Therefore, we are interested in the synthesis of modified nucleosides and their incorporation into DNA and RNA probes to identify their effects on DNA/RNA modifying enzymes, focusing on TET enzymes. A combination of organic chemistry, DNA solid phase synthesis and analytical methods, including HPLC and LC-MS/MS, enables comprehensive studies of TET enzymes *in vitro* and *in cellulo*. Additionally, the established methods facilitate the identification of potential TET inhibitors and may lead to the discovery of promising lead structures.

Cellular studies of novel synthetic 5mC analogues have shown significant effects on cell cycle regulation, strengthening their possible interaction with TET enzymes. Further investigation will help to identify their underlying mechanism of action and cellular consequences of TET inhibition.

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# PRECISION DRUGS: A COVALENT STRATEGY TO MINIMIZE SIDE EFFECTS OF PI3K INHIBITOR CANCER THERAPY

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Phosphoinositide-3-kinase (PI3K) signaling is a key regulator of cellular processes such as cell growth, proliferation and metabolism. Constitutively activated PI3K is frequent in tumors and drives cancer progression. PI3K is therefore broadly explored as therapeutic target, but many pan-PI3K inhibitors displayed a low response rate in clinical trials - mainly due to adverse side effects. Inhibition of PI3K using class I pan-PI3K inhibitors triggers a rapid increase in blood glucose and insulin.[1] Isoform-selective inhibition of PI3Kα might alleviate hyperglycemia and hyperinsulinemia, but the selectivity of claimed PI3Kα-specific drugs is currently limited. To date, the specific roles of the different PI3K isoforms (mainly PI3Kα and β) in insulin signaling remain controversial. A redundant physiological role of PI3Kβ in insulin action and sensitivity is under investigation.

Herein, we develop a rational approach to increase target selectivity exploiting a covalent binding of inhibitors targeting PI3K isoform-specific nucleophilic amino acid side chains. In PI3Kα, the non-conserved Cys862 is such a residue. A combination of warhead activity design, proximity and orientation allows a tight control of reversible inhibitor binding and isoform selective covalent binding. We have developed assays to characterize and select compounds *in vitro* and in cell. X-ray crystallography together with synthesis of the corresponding reversible analogs, washout experiments in SKOV-3 cells and nanoBRET experiments prove the covalent nature of the compounds. The development of isoform-selective covalent compounds represents a major step towards an increased local and temporal control of PI3K in precise and innovative cancer therapy, and has the potential to minimize metabolic side effects.

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# TOWARDS THE DISCOVERY OF BAY-850, A SELECTIVE AND CELL-ACTIVE ATAD2 CHEMICAL PROBE

**Kasia Borsuk (1), Vincent Rodeschini (1), Anne Brethon (1), Frédéric Frebault (1), Didier Roche (1), Jean-Yves Ortholand (1), Amaury E. Fernandez-Montalvan (2), Markus Berger (2), Benno Kuropka (2), Seong Joo Koo (2), Volker Badock (2), Joerg Weiske (2), Vera Puetter (2), Simon J. Holton (2), Detlef Stockigt (2), Antonius ter Laak (2), Jan Hubner (2), Hilmar Weinmann (2), Ingo V. Hartung (2), Matyas Gorjanacz (2), Matthew A. Clark (3), John W. Cuozzo (3), Ying Zhang (3), Anthony D. Keefe (3)**

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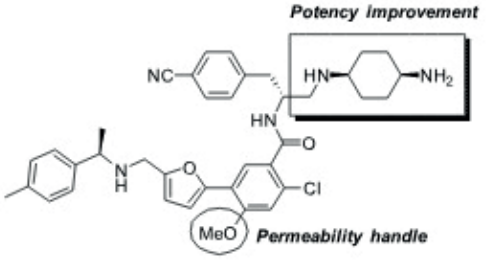
ATAD2 is an epigenetic regulator that binds to chromatin through its bromodomain. It´s overexpression has been associated with the progression of tumors and poor patient prognosis in various cancer types. However, ATAD2 has been considered as a difficult target, due to a predicted low druggability, and consequently, only a few inhibitors have been described to date.(1)

Here we report our medicinal chemistry approach that ultimately led to the discovery of BAY-850, a potent ($IC_{50}$ = 166 nM), selective and cell active inhibitor of ATAD2.(2) Extensive SAR study allowed the identification of a cyclohexyl diamine substituent, leading to a substantial potency improvement. The introduction of MeO substituent on the central phenyl ring was found to improve permeability.




BAY-850

| | |
|---|---|
| ATAD2 $IC_{50}$ (nM) | 166 |
| LogD (7.4) | 2.9 |
| LLE | 4.8 |
| Sw pH6.5 (mg/L) | > $3.10^3$ |
| Caco-2 (A-B, nm/s) | 39 |
| Efflux ratio | 0.3 |
| $CL_b$ (vitro, *h* liver microsomes) (L/h kg) | 1.5 |

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# HYBRID COMPOUNDS COMBINING PYRAZINAMIDE AND p AMINOSALICYLIC ACID AS MULTI-TARGET ANTITUBERCULARS: DESIGN, SYNTHESIS, AND ANTIMYCOBACTERIAL EVALUATION

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Tuberculosis is a classical disease for multi-target drug therapy. Conventional treatment consists of a combination of four different drugs either taken separatly or in fixed dose combination. Based on the fact that hyberdization is another multi-target drug design approach, we report the design, synthesis, and antimycobacterial evaluation of a series of hybrid compounds combing pyrazinamide, a first line antitubercular, and *p*-aminosalicylic acid, a second line antitubercular (Fig. below).[1,2] Compounds were synthesized by reacting different pyrazinecarboxylic acids, activated by 1,1'-carbonyldiimidazole, with *p*-aminosalicylic acid in dimethylsulfoxide as a solvent. Obtained compounds were then cyclized to form a lactone in the *p* -aminosalicylic acid fragment. Title compounds were *in vitro* evaluated for their antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv and four other non-tubercular mycobacterial strains. As complementary screening, final compounds were evaluated for antibacterial, antifungal, and cytotoxicity in HepG2 liver cancer cell line. Most compounds showed moderate to excellent antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv and *Mycobacterium kansasii* with no *in vitro* cytotoxicity. From obtained results, we could conclude that cyclized compounds were more active against the latter mycobacterial strains than their parent non-cyclic compounds (most active compound was 6-chloro-*N*-(4-oxo-4*H*-benzo[*d* ][1,3]dioxin-7-yl)pyrazine-2-carboxamide with minimum inhibitory concentration against *Mycobacterium tuberculosis* H37Rv ≤ 0.78 μg/mL). This finding is justified by decreasing the hydrophilicity and hence improving the penetration of compounds through the lipophilic mycolic cell walls of mycobacteria. No antibacterial or antifungal activities were observed for any of the prepared compounds.

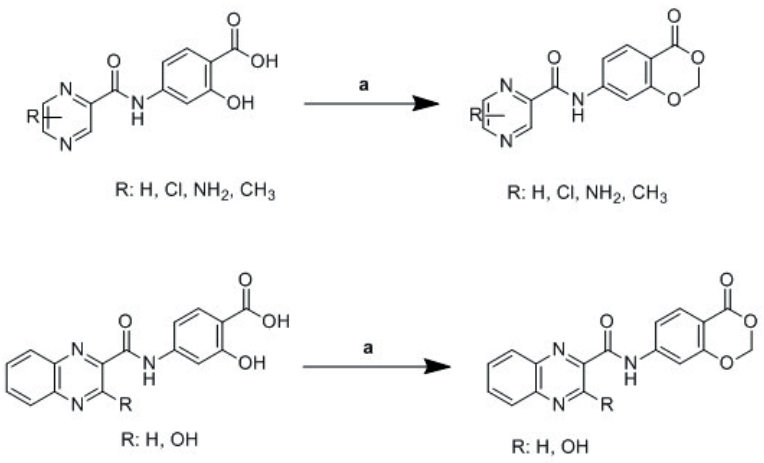


Fig.: The general structures of hybrid compounds combining pyrazinamide and *p*-aminosalicylic acid; a) $K_3PO_4$ .$3H_2O$, DCM, DMF, 100 °C, reflux for 10 hrs.

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# PHOTOLABELING OF GABA-A RECEPTOR BY NEUROSTEROID-BASED PHOTOPROBES

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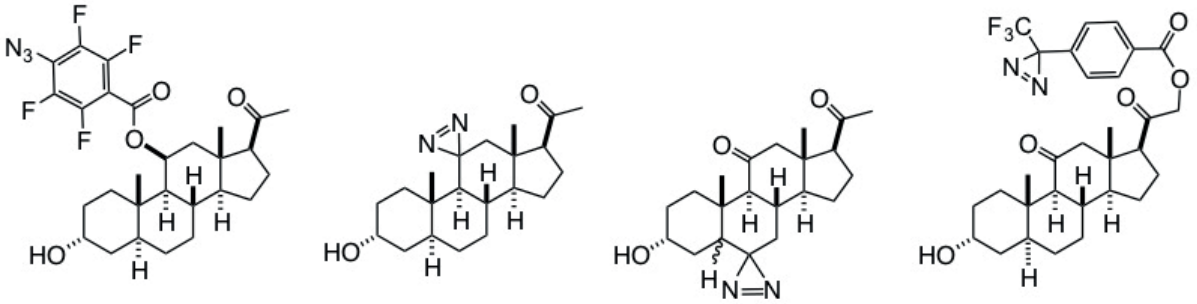
A native human brain GABA-A receptor is a collection of 19 molecular species comprising heteropentamers of several α, β, γ, δ and other protein subunits. GABA-A receptor is a macromolecular target of a large variety of popular CNS drugs that include general anesthetics, anxiolytics, antidepressants and sedatives. Many of these drugs bind inside the interfaces that separate the various subunits, and most are allosteric ligands that modulate the ion-channel function of the receptor. Up until this year, the paucity of structural data on the native brain receptor necessitated the use of mutational analyses and photolabeling techniques combined with homology models based on simpler bacterial orthologs to provide information on the location and the nature of the binding sites. In this work, our most recent results related to the design, synthesis and pharmacological evaluation of photaffinity probes based on the structures of endogeneous neurosteroids will be discussed. In photoprobes **1**-**5**, the photoreactive diazirine or azide residues were either attached as pendants or molded onto rings B, C or D of the steroid framework. Compounds **1** and **2** were not efficient protein photolabels despite their very strong positive modulatory activity[1] and compounds **3** and **4** were only weak allosteric agonits. In contrast, the photoaffinity analog **5**was a potent partial allosteric agonist that efficiently photolabeled the α1β3γ2L receptor.[2] The photolabeling was significantly or completely inhibited by other neurosteroidal allosteric modulators, such as alfaxalone and allopregnanolone, at concentrations close to their $EC_{50}$ values, but not by the inhibitory steroidal antagonist such as pregnenolone sulfate, or general anesthetics etomidate and barbiturate that bind to a different site. The potency and pharmacological specificity of photolabeling by compound **5** indicate its suitability for characterizing neurosteroid binding sites in native GABA-A receptors.

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# IN THE SEARCH OF POTENT AND SELECTIVE 5-HT7 RECEPTOR BIASED LIGANDS AMONG ARYLSULFONAMIDE DERIVATIVES OF (ARYLOXY)ALKYL ALICYCLIC AMINES

**Vittorio Canale (1), Grzegorz Satała (2), Rafał Kurczab (2), Andrzej J. Bojarski (3), Emilie I. Anderson (3), Lauren J. Laskowski (3), John D. McCorvy (3), Paweł Zajdel (1)**

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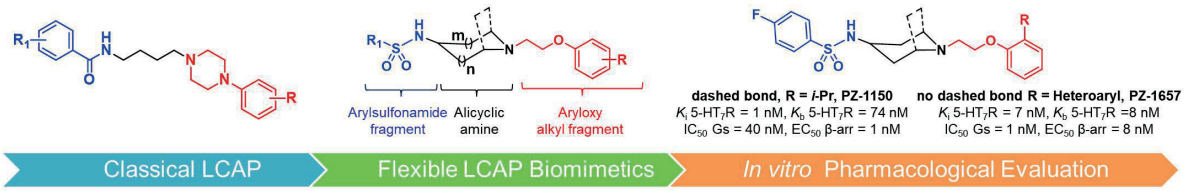
The 5-HT$_7$ receptor (5-HT$_7$R) represents the most recently identified member of the serotonin G protein-coupled receptor (GPCR) subtypes, which has been identified as a promising drug target for the treatment of affective disorders and neurodegenerative processes. Apart from the canonical G protein ($G_{\alpha s}$) coupling to adenylate cyclase (AC),[1] 5-HT$_7$R has recently been shown to recruit β-arrestin, which are involved in regulation of receptor desensitization, down-regulation, as well G protein-independent signalling pathways. [2] Thus, the development of 5-HT$_7$R ligands that differently engage distinct signalling events (known as functionally selective or biased ligands), could be considered a promising strategy to provide more efficacious new-generation drugs with reduced side effects.

We have recently designed and synthesized a novel class of 5-HT$_7$R ligands, namely arylsulfonamide derivatives of (aryloxy)alkyl alicyclic amines as flexible long-chain arylpiperazine (LCAP) biomimetics. Among tested derivatives, several compounds displayed high affinity for 5-HT$_7$R ($K_i$ < 50 nM) in radioligand binding experiments, and were selective over structurally related GPCRs and transporters (i.e., 5-HT$_{1A}$R, 5-HT$_{2A}$R, 5-HT$_6$R, D$_2$R, SERT, NET).[3,4]




Bioluminescence-based *in vitro* assays revealed that evaluated compounds decreased the constitutional $G_s$ -mediated cAMP production behaving as potent inverse agonist. Additionally, they were able to recruit β-arrestin recruitment displaying β-arrestin-biased agonist properties. Subsequent structure-activity relationship studies indicated that a kind of substituent in an *ortho* position at the aryloxy fragment of the structure seems to be more crucial for determining the β-arrestin-bias profile of evaluated compounds than the terminal arylsulfonamide moiety.

The study allowed for the identification of compounds PZ-1150 and PZ-1657 which could be regarded as potent β-arrestin biased ligands. Further studies focused on this class of biased 5-HT$_7$R ligands might provide a valuable chemical probe to better understand the relationship between G protein/β-arrestin signalling pathways and *in vivo* pharmacological effects of 5-HT$_7$R.

Aknowledgements: The study was supported by the National Science Center, Poland (grant no. DEC-2012/05/B/N27/03076) and by Jagiellonian University Medical College (grant no. K/DSC/005289).

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# DECIPHERING THE PROMISCUITY OF ANDROGRAPHOLIDE: LESSONS IN TURNING A VICE INTO A VIRTUE

**T.N. Quy TRAN (1), Ying Fu LIM (1), Kit Yarn WONG (1), Nur Fatima BAGINDA ALI (1), W.S. Fred WONG (2), Christina L.L. CHAI (1)**

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Natural products have been demonstrated to be good sources of lead compounds for drug discovery and development. However, a significant number of natural products are promiscuous and are known to target multiple biological targets, which in turn may account for their varied pharmacological activities. In the context of the single target paradigm of drug discovery, promiscuity is *not* a desirable attribute. However, it has become increasingly apparent that for some diseases, multi-targeting drugs are needed for effective therapy. This would necessitate the development of drugs that can target multiple targets with the desired polypharmacological properties ('beneficial' promiscuity). One natural product that been shown to possess a range of pharmacological activities, from anti-cancer to anti-inflammatory properties, is andrographolide. Andrographolide is the main bioactive constituent of *Andrographis Paniculata*, a herb used in traditional Chinese and Ayuverdic medicines for decades. Despite the continuing interest in this natural product, there is little understanding on the polypharmacological activities of andrographolide. This presentation describes our efforts directed towards deciphering the promiscuous behavior of andrographolide. This knowledge is critical in the exploitation of andrographolide as a lead compound in drug discovery.

# DISCOVERY AND OPTIMIZATION OF A NEW CLASS OF POTENT AND NON-CYTOTOXIC TRYPANOSOMA BRUCEI GROWTH INHIBITORS

**Alina Ciammaichella, Jesus M. Ontoria, Federica Ferrigno, Melania D'Amico, Andreina Basta, Ilaria Biancofiore, Giacomo Paonessa, Alberto Bresciani, Edith Monteagudo, Annalise Di Marco, Vincenzo Summa, Steven Harper**

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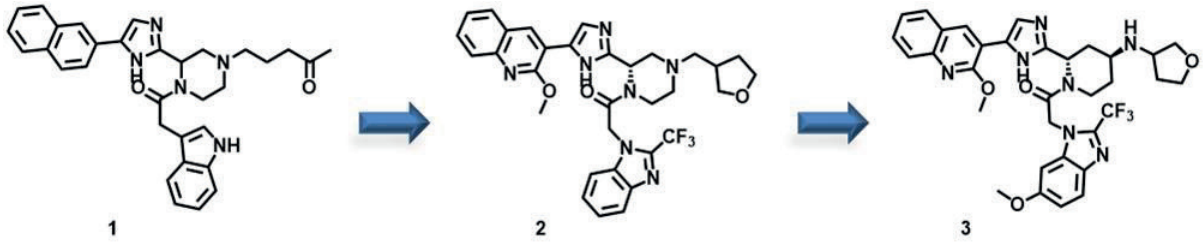
Human African Trypanosomiasis (HAT), also known as sleeping sickness, is a parasitic disease transmitted to humans by tse-tse fly that causes significant mortality in sub-Saharan Africa. Over 65 million people living in endemic areas are at risk of contracting HAT and about 5000 new HAT cases are reported annually. HAT disease progression involves two stages, the first of which is characterized by the spread of the parasite in the blood and in the lymphatic system. The second more severe stage of the disease occurs after the parasite crosses the blood-brain barrier into the CNS (central nervous system). After the parasite has entered the CNS it causes poor coordination, dramatic mood swings, confusion and convulsions, and if untreated this stage of the disease is always fatal. Current treatments (nifurtimox-eflornithine combination therapy, melarsoprol) require hospitalization, are toxic and are not effective against the second stage of the disease, highlighting the need for novel orally administrable treatments.




Here we report the discovery of a new series of *T. brucei* growth inhibitors by screening and describe our lead optimization efforts in this area. Screening of a subset of compounds from our internal collection in a whole parasite growth assay led to the identification of compound **1** ($EC_{50}$ = 490 nM) as a novel, selective and non-cytotoxic *T. brucei* growth inhibitor. Preliminary SAR on the hit compound **1** strongly improved growth inhibition potency and led to compound **2** that showed low nanomolar activity ($EC_{50}$ = 29 nM), no cytotoxicity (HeLa $CC_{50}$ > 25000 nM), and that had good blood-brain barrier permeability. However, **2** was rapidly metabolized in mouse hepatocytes, meaning that our lead optimization efforts focused on aligning the high potency of **2** with improved *in vitro* metabolic stability. This work led ultimately to the identification of compound **3** ($EC_{50}$ = 7 nM) and both the SAR, leading to this compound, and its biological and pharmacokinetic profiles will be described.

# TARGETED IMAGING AGENTS FOR CANCER DIAGNOSIS AND SURGERY

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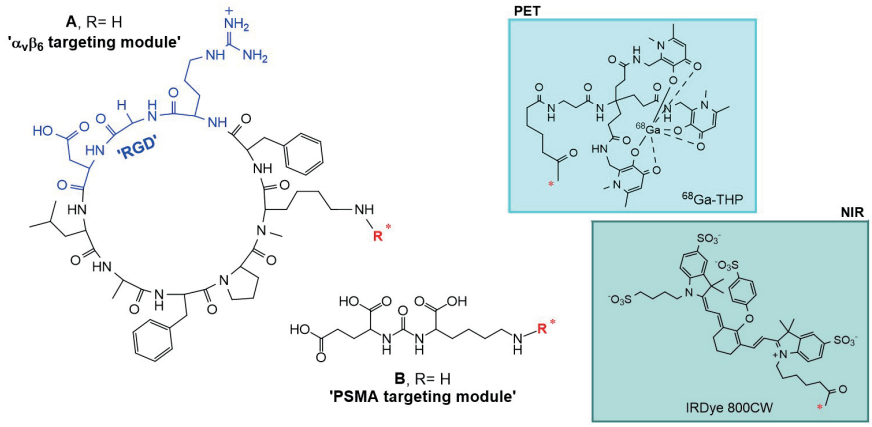
Medical imaging has undergone major advancements in recent years and the amount of information that can be obtained for various pathological and/or physiological conditions has markedly improved clinical performance. Near-infrared (NIR) fluorescence imaging and radionuclide imaging are two relatively new technologies, which have complemented the range of more conventional techniques, such as X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound systems.[1]

Current methods used to distinguish cancer tissues from normal tissues are based on imaging techniques and several imaging agents have been developed for 'image-guided' diagnosis and/or surgery procedures. Both NIR fluorescence imaging and radionuclide imaging have demonstrated tumour detection with high sensitivity.[2] Simultaneous use of these two techniques would in principle allow multimodality visualisation, as well as complementary diagnostic information (i.e. pre-operative planning, *via* positron-emission tomography (PET) imaging) and intra-operative tumour localisation (*via* NIR imaging) for increased surgical precision.

In this context, our research focuses in the synthesis, biological validation and clinical translation of new NIR optical probes and PET radiopharmaceuticals in relation to pancreatic and prostate cancer. On the basis of previous work, we have identified selected targeting modules (A and B) which have high affinity for specific biological targets in tumour cells, i.e. prostate-specific membrane antigen (PSMA, overexpressed in prostate cancer)[3] and integrin $\alpha_v\beta_6$ (overexpressed in pancreatic cancer).[4]




Studies will be described that relate to the development of new PSMA- and $\alpha_v\beta_6$-targeted agents for NIR and PET imaging. These bear specific optical tags (e.g. IRDye® 800CW) or hexadentate tris(hydroxypyridinone) (THP)-based chelators (for $^{68}$Ga-radioisotope)[3] attached to either structure A or B. *In vitro* validation demonstrates that these imaging agents possess a high affinity for the targets of interest. Preclinical *in vivo* validation highlights that an optimal biodistribution is found for some of these various conjugates in xenograft mouse models of cancer. This research highlights the potential of multimodality visualisation in clinical settings, through efficient imaging agents for cancer diagnosis and surgical intervention.

Theragnostis Ltd (https://theragnostics.com/) is gratefully acknowledged for financial support.

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# IDENTIFICATION OF INTERFACE INHIBITORS OF THYMIDYLATE SYNTHASE AS ANTICANCER AGENTS AND FRET-BASED INTRACELLULAR TARGET ENGAGEMENT

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Thymidylate synthase is an important target for anticancer therapy [1]. Classical inhibitors as anticancer drugs show rapid drug resistance development. We have identifed the **LR octapeptide** (Leu-Ser-Cys-Gln-Leu-Tyr-Gln-Arg) as a TS dimer interface binder (allosteric inhibitor) that, by stabilizing the di-inactive TS form, affects protein catalytic activity and increase phosphorylation [2].

[image]

The mechanism of action has never been proposed before in 60 years after 5Fluorouracil (5FU) was discovered. LR peptide and derivatives induce cancer cells growth inhibition in platinum-sensitive and -resistant ovarian cancer and other cancer cell models. Structural informations from X-ray crystal structures shows unambiguosly where the peptides binds at the protein interface. Mass Spectrometry proteomic studies demonstrate a different proteome modulation for the peptides with respect to small molecule inhibitors. Lr peptides do not increase TS levels, reduces dhydrofolate reductase (DHFR) and modulates other proteins (HSP90, GARFT, HSP90, TRAP1) in a statistically validated way [3]. These proteins represent a validated set that can work as biomarkers of the cellular activity. Specificity of peptides as drugs is one of the important issues that halt their development process, therefore we developed a specific assay by adopting FRET technology based on the tertracysteine protein mutants (CCPGCC arsenic-binding domain construct at the N terminus) ability to bind agreen-emitting fluorescein-based diarsenical probe. Target engagement studies using a cellular FRET assay was set up in which we demonstrated that the fluorescent hilyte405 -LRpeptide specifically interacts with TS in the cells with high specificity (only 5% of the inhibitor did not bind TS) [4]. Starting with the cell lysate, we were able to develop live cell assay and characterize the cellular targeting after 48 hours of treated/untreated cancer cells growth.

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# DESIGN, SYNTHESIS AND PHOTOCHEMICAL PROPERTIES OF A NEW PHOTOSWITCHABLE TRPV6 INHIBITOR

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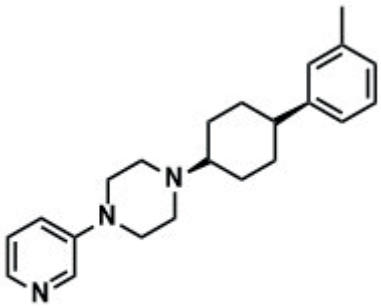
Since their discovery, the TRP family of $Ca^{2+}$ transporters became an interesting target due to its involvement in a diverse number of diseases [1]. One of its representatives, TRPV6 arouse as a key point in cancer progression, however, the physiopathological mechanisms remains unclear [2]. One effective strategy to access the spatiotemporal control of a chosen protein is to attach light responsive groups to known ligands [3]. To enable this approach, we incorporated the azobenzene moiety to *cis*-22a, a potent TRPV6 inhibitor previously discovered in our group [4]. Remarkably, we found a derivative that inhibited TRPV6 in micromolar range ($IC_{50}$ = 1.70 ± 0.36 µM) and possess the required photoswitchable profile for its precise spatiotemporal control. This compound will now be used to deepen our understanding of TRPV6 mechanisms at the cellular level.



***cis*-22a**
$IC_{50}$ = 0.32 ± 0.12 µM

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# A POTENT SERIES TARGETING THE MITOCHONDRIAL ELECTRON TRANSPORT CHAIN WITH DUAL STAGE ANTIMALARIAL ACTIVITY

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The mitochodrial electron transport chain (mETC) is a promising therapeutic target to develop new antimalarials, due to its essential role in the *de novo* pyrimidine biosynthesis by the malaria parasites 1). Despite the interest in the development of new mETC inhibitors, a limited number of new chemical entities have identified to interact with this multicomponent target.
In this communication we report the results from a medicinal chemistry programme focused on a pyrroloquinolone series **1**, targeting the *Plasmodium falciparum* mETC. This novel series **1** was tested against blood- and liver-stage malaria parasites and our hit compound revealed excellent dual-stage inhibitory activity. The structure-activity relationships and the inhibition of mETC components (cytochrome $bc_1$, dihydroorotate dehydrogenase) will be discussed in this communication (**Figure 1**). In addition, our hit compound interferes with calcium homeostasis in transgenic malaria parasites. In addition, these compounds also revealed a good selectivity index, *in vivo* efficacy and favourable pharmacokinetic properties.

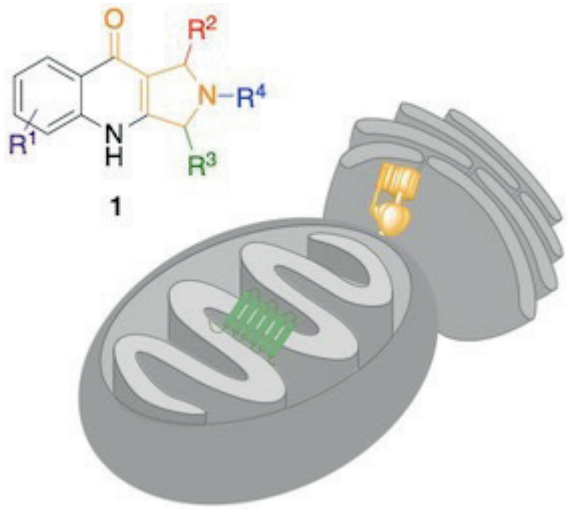


**Figure 1** Structure of the mETC inhibitor **1** and representation of their potential targets

**Acknowledgements**

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# SPECTRAL CYTOMETRY & DRUG SCREENING - PHARMACOLOGICAL STUDY OF P2RX7

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P2RX7 receptor belongs to the family of P2X purinoreceptors and binds ATP with low affinity. P2RX7 is a non-selective cation channel, activated in two steps. Short ATP exposure triggers opening of P2RX7 channel and a rapid $Ca^{2+}$ influx ($Na^{+}$ or $Ca^{2+}$ influx / $K^{+}$ efflux). The second step is activated upon sustained ATP exposure and relies on the formation of a non-selective large pore, permeable to molecule up to 900kDa. P2RX7 is involved in the control of proliferation, cell death, inflammation and in numerous physiopathology mechanisms, especially cancer, Alzheimer disease and chronic inflammation. Nowadays, there is an increasing interest for developing P2RX7 modulators in therapeutics. Actually, agonists represent an interesting approach as anticancer drugs, whereas antagonists may be useful as anti-inflammatory drugs. In this context, sharp screening of candidate molecule potency is of major interest. P2RX7 pharmacology has been intensely studied by electrophysiology methods, such as patch-clamp, or by the use of fluorescent dyes coupled to microscopy or plate reader analysis. In this study, we used flow cytometry to simultaneously assess the $Ca^{2+}$ influx, large pore opening and cell viability upon BzATP-mediated P2RX7 activation. Flow cytometry gives the advantage to get rid of dead cells that interfere with the measurement of large pore opening (false positive). Quantification of double positive cells (high $Ca^{2+}$ and large pore opening) proves to be an excellent method for compound screening and measurement of potency ($EC_{50}$, $IC_{50}$) of both agonistic/antagonistic molecules. However, fluorescence measurement may be impeded by the intrinsic fluorescence of tested compounds. In this study, we used spectral cytometry to manage the intrinsic fluorescence of tested compounds that may interfere with the biological assay. Spectral cytometry allows simultaneous measurements of several biological activity along with the management of the intrinsic fluorescence of the tested compounds and then represents a new analytical tool for the screening of drug candidates.

# DUALLY ACTING MAO-B/5-HT6 RECEPTOR MODULATORS WITH POTENTIAL APPLICATION IN NEURODEGENERATIVE DISORDERS

**Vittorio Canale (1), Katarzyna Grychowska (1), Abdul Raheem Keeri (1), Grzegorz Satała (2), Agnieszka Olejarz (3), Marcin Drop (1), Paulina Koczurkiewicz (4), Rafał Kurczab (2), Martyna Krawczyk (5), Elżbieta Pękala (4), Andrzej J. Bojarski (2), Tadeusz Karcz (3), Piotr Popik (5), Paweł Zajdel (1)**

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Alzheimer's diseases (AD) is a an age-related progressive neurodegenerative disorder and represents the most common cause of dementia associated with the loss of cognitive function, and behavioral disturbances. Due to the complex etiology of AD, the design of multi-target functional ligands represents an attractive and widely adopted approach.[1]

Our strategy consists in the development of dually acting compounds which could relieve cognitive impairment by modifying 5-$HT_6$R-mediated transmission and additionally display neuro-protective properties by monoaminooxygenase B (MAO-B) blockade.[2,3] In this context an approach, including *in silico* structure optimization, was applied for the design of novel class of compounds combining indole-based scaffold present 5-HT6R ligands with known MAO-B pharmacophore fragments.

The study allowed for the identification of potent dually acting compounds capable of inhibiting MAO-B and targeting 5-$HT_6$R (displaying affinity for both targets in nanomolar range) with acceptable selectivity over structurally related GPCRs and MAO-A. Neuroprotective properties of the most interesting compound were assessed in MTT test.

A better understanding of effects produced by MAO-B/5-$HT_6$R modulators may impact future development of neurodegenerative-directed treatment strategies.

**Acknowledgements**: The study was financially supported by National Science Centre, Poland (grant no. 2016/21/B/NZ7/01742).

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# CHEMICAL BIOLOGY ENABLING DRUG DISCOVERY. DEVELOPMENT OF CNS PENETRANT, SMALL MOLECULE INHIBITORS OF THE WNT-DEPALMITOLEATING ENZYME NOTUM

**James Sipthorp (1,2), Will Mahy (1), Nicky Willis (1), Elliott Bayle (1,2), Sarah Frew (1), Amy Monaghan (1), Sarah Jolly (1), Magda Bictash (1), Yuguang Zhao (3), Luca Vecchia (3), Reinis Ruza (3), Steve Howell (2), Bram Snijders (2), Paul Whiting (1,4), J. P. Vincent (2), E. Yvonne Jones (3), Paul V. Fish (1,2)**

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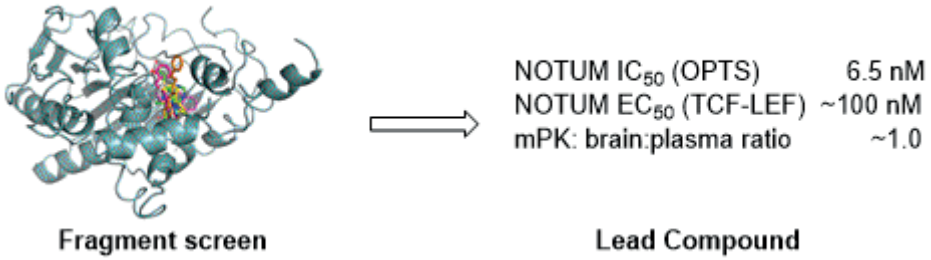
Members of the Wnt family are secreted signalling proteins that play key roles in adult stem cell biology as well as in embryonic development. Conversely, dysregulation of Wnt signalling is frequently associated with growth-related pathologies and cancers, particularly those of tissues for which Wnts normally stimulate self-renewal and repair. Wnt signalling is also implicated to have a role in neurodegenerative diseases such as Alzheimer's disease (AD). Cognitive impairments, characteristic of AD, correlate closely with the loss of synapses and current knowledge suggests that excess amyloid-β (Aβ) causes synapse dysfunction by impairing synapse maintenance, at least in part, through causing dysfunction of Wnt signalling. Compromised Wnt signalling may also be associated with AD through loss of blood-brain barrier (BBB) integrity and Aβ generation through β-sectretase expression.

*O*-Palmitoleoylation of a conserved serine residue in Wnt proteins is a key post-translational modification (PTM) required for efficient binding of Wnt proteins to Frizzled receptors, a requirement for signal transduction. A carboxylesterase NOTUM has been shown to act by mediating the depalmitoleoylation of Wnt proteins resulting in suppression of Wnt signalling.[1] We have shown that *notum* is expressed in the mammalian central nervous system (CNS): *notum* is upregulated at mRNA level in whole brain lysates in AD model (APP-PS1 mice); and upregulated in human AD patient brain samples. It follows that inhibition of NOTUM could restore Wnt signalling with potential benefit in disease where Wnt deficiency is an underlying cause. Hence, our objective was to discover inhibitors of NOTUM suitable for exploring the regulation of Wnt signalling in the CNS and modulation of AD phenotypes.

In order to identify new small molecule inhibitors of NOTUM, a crystallographic fragment screen was performed using the XChem platform at Diamond Light source. Fragments observed to bind in the palmitoleate pocket were all re-synthesised to confirm structure and establish inhibition of NOTUM carboxylesterase activity. Preferred fragments hits (1-50 μM) were optimised by SAR studies guided by SBDD to give potent inhibitors of NOTUM (< 10 nM) with excellent CNS penetration.




This presentation will focus on our work using activity based probes (ABP) that react specifically with serine hydrolases. These ABPs have been used to determine target engagement and enzyme occupancy of NOTUM in a cellular context. Compound selectivity across the hydrolase family has also be assessed using quantitative chemical proteomics. These techniques will guide our efforts to develop a 'fit-for-purpose' NOTUM inhibitor to determine its function in the CNS and therapeutic potential in AD.

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# NEUROTRANSMITTER-RESPONSIVE NANOSENSORS FOR MAGNETIC RESONANCE IMAGING

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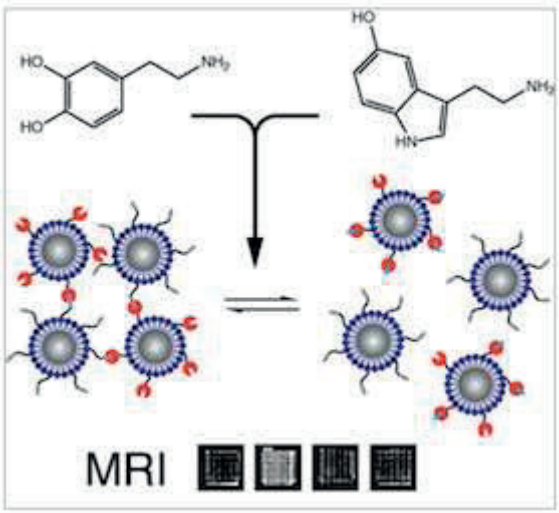
Neurotransmitter-sensitive contrast agents for magnetic resonance imaging (MRI) have recently been used for mapping signaling dynamics in live animal brains, but current paramagnetic sensors for $T_1$-weighted MRI are effective only at micromolar concentrations that themselves perturb neurochemistry. Here we present an alternative molecular architecture for detecting neurotransmitters, using superparamagnetic iron oxide nanoparticles conjugated to tethered neurotransmitter analogs and engineered neurotransmitter binding proteins. Interactions between the nanoparticle conjugates result in clustering that is reversibly disrupted in the presence of neurotransmitter analytes, thus altering $T_2$-weighted MRI signals. We demonstrate this principle using tethered dopamine and serotonin analogs, together with proteins selected for their ability to competitively bind either the analogs or the neurotransmitters themselves. The corresponding sensors for dopamine and serotonin exhibit relaxivity changes of up to 20% and selectivity for their targets versus other monoamines. Importantly, they also operate at nanomolar levels, with neurotransmitter binding capacities below endogenous neurotransmitter concentrations. Semisynthetic magnetic particle sensors thus represent a promising path for minimally perturbative molecular MRI-based studies of neurochemical analytes in the brain.[1]

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# METAL-CHELATING AGENTS WITH DUAL INHIBITORY ACTIVITY AGAINST HEPATITIS C AND DENGUE VIRUSES

**Erofili Giannakopoulou (1), Vasiliki Pardali (1), Efseveia Frakolaki (2), Vassilios Myrianthopoulos (1), Emmanuel Mikros (1), Ralf Bartenschlager (3), Niki Vassilaki (2), Grigoris Zoidis (1)**

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Hepatitis C Virus (HCV) infections pose a major public health threat globally, with infected individuals being at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. Despite the great advances in treatment options, patients may still not have access to effective treatments due to high cost. Moreover, current chemotherapy is associated with numerous side effects and viral resistance, and without a vaccine at the horizon, the global burden of HCV infections remains high.[1]

Dengue (DENV) is a mosquito-borne viral infection that causes widely distributed and endemic, visceral and central nervous system diseases and can give rise to dengue hemorrhagic fever or dengue shock syndrome. The global incidence of Dengue has grown dramatically in recent decades, but despite the extensive research there is no clinically approved therapy, thus, it constitutes high priority target for drug discovery.[2]

Based on literature reports on metal-chelating antivirals[3] we have previously designed and synthesized novel indole-diketopiperazine heterocycles with activity against Hepatitis C virus.[4] Trying to investigate the role of the metal binding group, we performed several structural modifications aiming to obtain a novel class of metal chelators with ability to inhibit HCV proliferation.

Here we report the design and synthesis of a series of compounds described as bicyclic-substituted hydantoin analogues. By utilizing a structure-based approach, several substituents were incorporated to the lead compounds, which, along with the performed docking-scoring calculations, were used to better characterize the Structure-Activity Relationships of the synthesized derivatives.

All the novel synthesized compounds were fully characterized and evaluated for their effect on HCV RNA replication and cell viability exhibiting really low $EC_{50}$ values, which was a marked improvement over that of the parent compounds. As DENV and HCV are members of the Flaviviridae family and they share several similarities, the synthesized compounds were evaluated against DENV as well. Biological results suggest that the novel class of the metal-chelators, presented herein, offers a highly promising starting point for the design of potent multi-targeted antiviral agents.

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# A NOVEL IN VITRO TOOL FOR THE ASSESSMENT OF BLOOD-BRAIN BARRIER PERMEABILITY

**Justyna Godyń (1), Dominika Gucwa (1), Tereza Kobrlova (2), Martin Novak (2,3), Ondrej Soukup (2), Barbara Malawska (1), Marek Bajda (1)**

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Profiling blood-brain barrier permeability of bioactive molecule at an early drug development stage is a part of the optimization process of a compound's physicochemical properties, and hence pharmacokinetic profile. Presented study was focused on the development of a new *in vitro* method for assessment of compound's brain penetration. The tool is proposed as an alternative to the widely used PAMPA-BBB assay[1] (Parallel Artificial Membrane Permeability Assay for Blood-Brain Barrier) and based on a capillary electrochromatography (CEC) technique. It takes advantage of liposomes as structural substitutes of biological membranes, which are used as a capillary inner wall coating material. Following optimization of analysis conditions, migration times for a set reference drugs (mainly non-ionized in pH 7.4) were examined in a liposome coated capillary. On that basis, the retention factor (log k) was determined for each reference drug. Obtained log k values and experimentally received reference permeability parameters: log BB (*in vivo* data) and log $P_e$ (PAMPA-BBB data) were compared with one another. Correlation coefficients were calculated, giving comparable results for CEC log k/log BB and analogical PAMPA-BBB log $P_e$/log BB analyses. Approximate ranges of log k for the central nervous system (CNS) permeable (CNS(+)) and non-permeable (CNS(–)) drugs were established. The new method has the potential to work well as a simple tool for early BBB permeability assessment of research compounds. It is an innovative, fast and relatively cheap alternative to the PAMPA-BBB technique.

| | acetaminophen | alprazolam | aminophenazone | antipyrine | barbital | caffeine | carbamazepine | cetirizine | cyclobarbital | diazepam | digoxin | fexofenadine | fluconazole | hexobarbital | hydrocortisone | lamotrigine | levodopa | midazolam | norfloxacin | omeprazole | oxazepam | phenytoin | progesterone | theobromine | theophylline | zolpidem |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CNS +/– classification[a)] | + | + | + | – | + | + | + | – | + | + | – | – | + | + | – | + | – | + | – | + | + | + | + | ± | – | + |
| CEC[b)] | + | + | ± | ± | + | – | + | + | + | + | – | – | ± | + | ± | + | + | + | – | + | + | + | + | ± | + | – |
| PAMPA-BBB[c)] | – | + | + | – | – | ± | + | ± | – | + | – | + | + | + | ± | + | + | + | – | + | + | + | + | – | – | + |

[a)] **literature data**
[b)] **log k ranges: CNS(+) log k > -1.61; CNS(–) log k < -1.84; CNS(±) -1.84 < log k < -1.61**
[c)] **log $P_e$ ranges: CNS(+) log $P_e$ > -5.398; CNS(–) log $P_e$ < -5.699 ; CNS(±) -5.699 < log $P_e$ < -5.398**

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# c-RAF KINASE INHIBITOR AS LEAD TO PHOTOSWITCHABLE SIRTUIN INHIBITION

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Sirtuins are a family of highly conserved NAD$^+$-dependent $N^{\varepsilon}$-acyl-lysine deacylases (KDACs). In general, these enzymes catalyse the transfer of acyl-groups from lysine side chains of substrate proteins onto ADP-Ribose (ADPR), releasing 2′-*O*-acyl-ADPR and the endogenous pan-sirtuin inhibitor nicotinamide as byproducts.[1]

Of the seven human sirtuins known, Sirt1–3 share deacetylase activity but differ in terms of intracellular location and substrate specificity. Hence, inhibition of Sirt1 and Sirt2 has been shown to produce beneficial effects in neurodegenerative diseases like Huntington's and Parkinson's disease, whereas Sirt3 activity was found to play an important role in cardiovascular diseases and age-extension in humans. Regarding tumorigenesis, the influence of sirtuins is inconsistent and subject of intensive investigation.[1]

Herein we present photoswitchable sirtuin inhibitors derived from the moderately active stilbene lead-structure **1** published as c-RAF inhibitor by GSK in 2006.[2] Synthetic modification yielded bistable photoswitches **2** and **3**, configuration of which could be repeatedly toggled by short term UV-A or visible light radiation, leading to specific changes in sirtuin inhibition and subtype affinity. The inhibitory activity against three human sirtuin isoforms (Sirt1–3) was tested in a fluorescence-based assay using $N^{\alpha}$-Boc-$N^{\varepsilon}$-acetyl-L-lysine 7-amido-4-methylcoumarin as substrate.[3] External light stimuli altered enzyme affinity represented by an increase or decrease of $IC_{50}$ values. These findings may lead to new, powerful tools in the elucidation of the molecular mechanism by which sirtuins exert their biological effects.

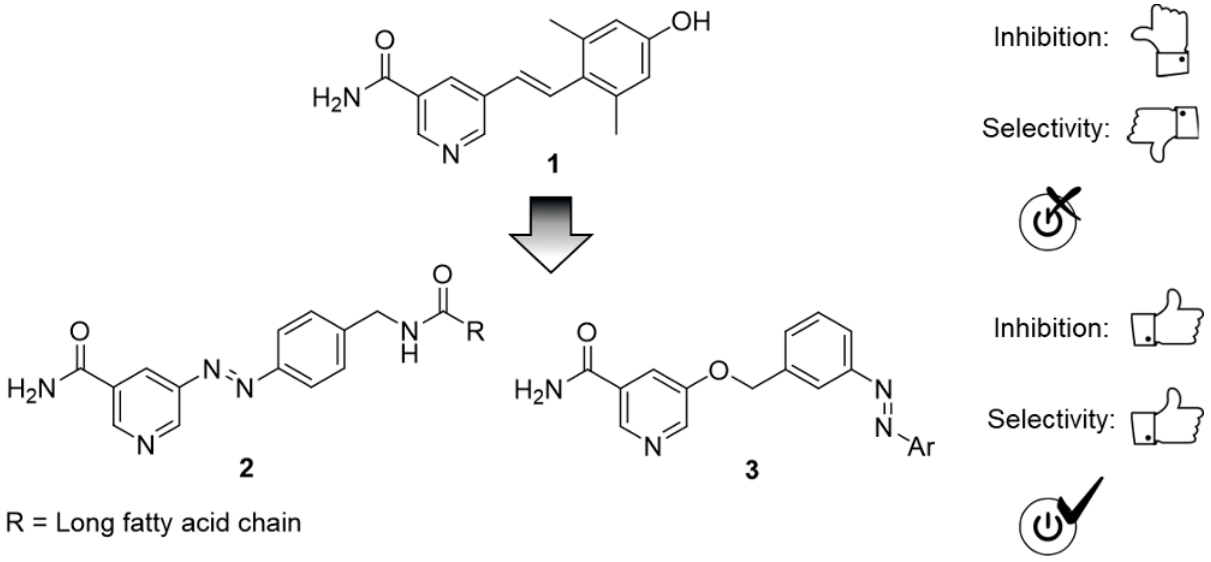


**Figure 1.** Lead-structure **1** and diazeno-based photoswitchable sirtuin inhibitors **2** and **3**.

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# DEVELOPMENT OF TORIN2 PHOTO-AFFINITY PROBES FOR TARGET IDENTIFICATION IN P. FALCIPARUM

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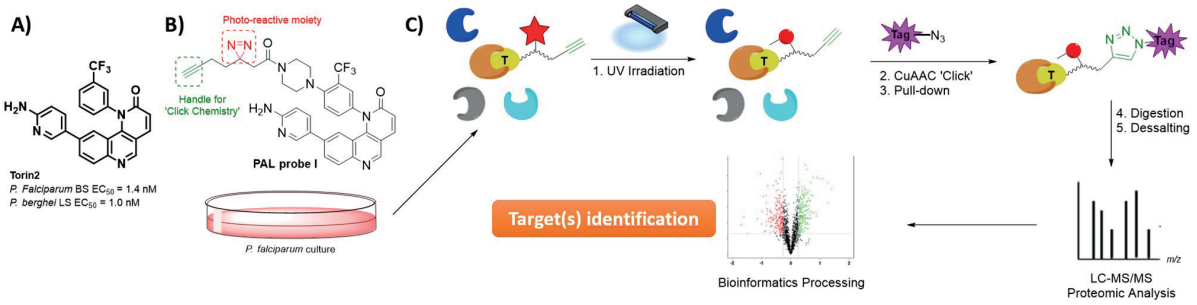
Malaria, the mosquito-borne infectious disease caused by protozoan parasites of the *Plasmodium* genus, is an endemic disease in most tropical regions of the globe that, despite the steady investment of the last decade, still represents a major public health concern with nearly half a million deaths a year and the last five years showing no reduction in the number of diagnosed cases. [1]

To overcome the need for drugs that act by different mechanisms than the ones currently in use, we have already shown that Torin2, a known ATP-competitive mTOR kinase inhibitor [2], is a potent antimalarial with in vivo activity against both liver and blood stages, that is independent of the hosts mTOR pathway [3]. Although no *Plasmodium* orthologs of mTOR exist, some proteins with high similarity sequences exist in the parasite proteome, mainly at the kinase catalytic domain, corroborating the hypothesis that Torin2 acts by a different mechanism of action compared to the drugs currently in the clinic.

Herein, we will report the development of photoaffinity-based probes, achieved through the functionalization of the Torin2 core structure with a photo-reactive moiety and a 'click chemistry' handle; and their application in a mass spectrometry-based proteome profiling assay in *P. falciparum* lysates and live cultures. (Scheme 1) Furthermore, we will disclose for the first time the results obtained in the identification of the target(s) of this potent class of inhibitors. These findings will enable the optimization of Torin2-based compounds as new antimalarials with a distinct mode of action to the drugs currently in clinical use, a key milestone to fight established parasite resistance.




Scheme 1: A) Torin2 hit compound; B) Structure of the Photo-affinity 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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# DUAL 5-HT6 AND D3 RECEPTORS ANTAGONISTS IN A GROUP OF 1H-PYRROLO[3,2-C]QUINOLINES WITH NEUROPROTECTIVE AND PRO-COGNITIVE ACTIVITY

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Cognitive impairment, which involves decline in learning and memory processes, is a common feature of neurodegenerative and psychiatric diseases.[1] In the search of novel therapeutic strategies for cognitive disorders, simultaneous pharmacological blockade of serotonin 5-$HT_6$ and dopamine $D_3$ receptors is considered as a promising approach.

Herein we present the design, synthesis and pharmacological evaluation of *N*-alkylated analogs of CPPQ ((S)-1-[(3-chlorophenyl)sulfonyl]-4-(pyrrolidine-3-yl-amino)-1H-pyrrolo[3,2-c]quinoline), previously described as a neutral 5-$HT_6$ R antagonist ($K_i$ = 3 nM, $K_b$ = 0.41 nM).[2] As shown by *in vitro* experiments, supported by quantum chemical calculations and molecular dynamic simulations, introducing alkyl substituents at the pyrrolidine nitrogen of CPPQ, fulfilled structural requirements for simultaneous modulation of 5-$HT_6$ and $D_3$ receptors.

The study identified compound **19** ((*S*)-1-((3-chlorophenyl)sulfonyl)-*N*-(1-isobutylpyrrolidin-3-yl)-1*H*-pyrrolo[3,2-*c*]quinolin-4-amine), which was classified as a dual 5-$HT_6$/$D_3$Rs antagonist ($K_{i\ (5\text{-}HT6)}$ = 27 nM, $K_{i\ (D3)}$ = 7 nM). Compound **19** behaved as a neutral antagonist at $G_s$ signaling and had no influence on receptor-operated, cyclin-dependent kinase 5 (Cdk-5) neurite growth.

In contrast to the well characterized 5-$HT_6$R inverse agonist intepirdine, compound **19** displayed neuroprotective properties against astrocyte damage induced by doxorubicine, as shown using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) staining to assess cell metabolic activity and lactate dehydrogenase (LDH) release as an index of cell membrane disruption. Biological results obtained for **19** in *in vitro* tests, translated into pro-cognitive properties in phencyclidine (PCP)-induced memory decline in the novel object recognition (NOR) task in rats.

The study was financed from National Science Center, Poland (Grant No 2016/21/B/NZ7/01742) and Jagiellonian University Medical College (Grant No K/DSC/004286).

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# HYBRIDS OF TAXIFOLIN AND PHENOLIC ACIDS – IN VITRO ASSAYS REVEAL OVERADDITIVE NEUROPROTECTION

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Natural products hold considerable interest for the development of novel neuroprotectants.Their properties counteract neurotoxic oxidative stress, one of the main hallmarks of neurodegenerative diseases. Based on promising results for 7-*O*-esters of the flavonolignan silibinin [1], hybrids of the lower molecular weight flavonoid taxifolin were synthesized to give more “drugable” compounds. Using phenolic acids cinnamic and ferulic acid, their 7-*O*-esters of taxifolin show pronounced and overadditive neuroprotective effects compared to the respective equimolar mixtures in the oxytosis assay using murine hippocampal HT-22 cells. To further examine the pharmacological profile of the 7-*O*-esters of taxifolin and their relevance in the context of Alzheimer’s disease [2], the compounds were then investigated in a phenotypic screening approach and applied to a set of *in vitro* assays related to neurodegeneration and aging [3].

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

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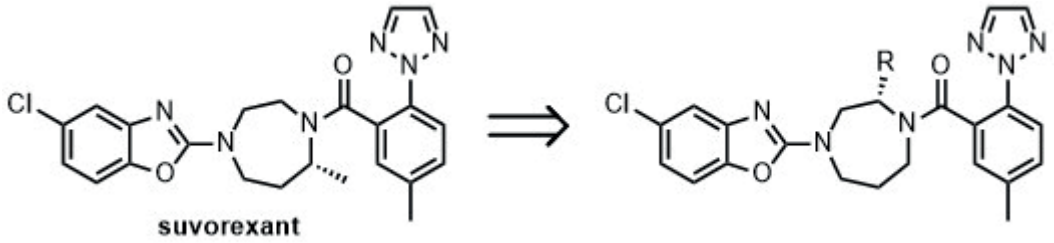
Orexins are neuropeptides that activate the rhodopsin-like G protein-coupled receptors OX1R and OX2R. The orexin system plays an important role in the regulation of the sleep-wake cycle and the regulation of feeding and emotions. The high resolution crystal structures of both receptor subtypes bound 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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# TARGETING LSD1 IN CANCER CELLS BY NITROREDUCTASE-MEDIATED PRODRUG ACTIVATION

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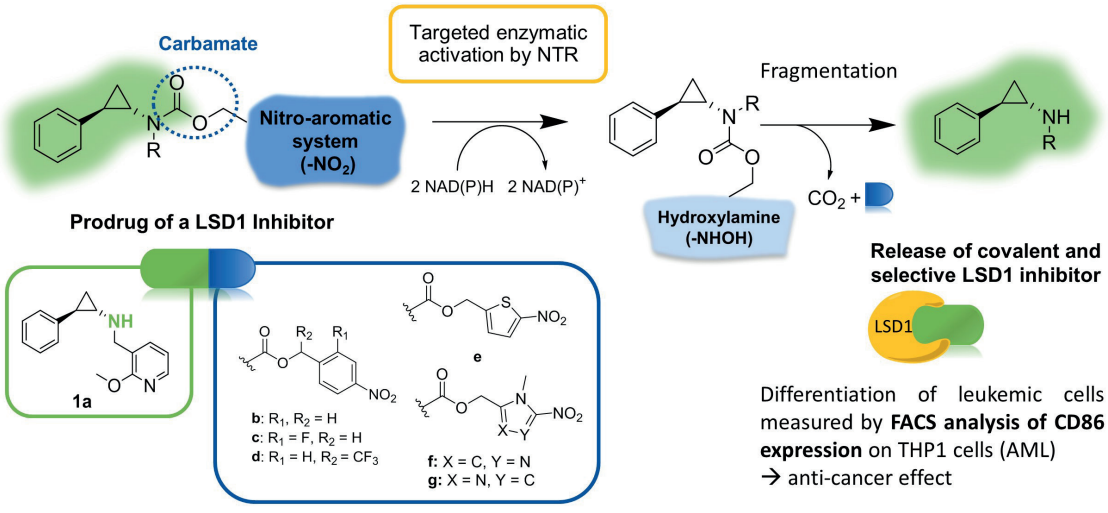
The lysine-specific demethylase 1 (LSD1 or KDM1A) has emerged as a highly promising therapeutic target in human malignancies and several drugs are already under current investigation in clinical trials. LSD1 is also established as a key effector of the differentiation block in acute myeloid leukemia (AML), which may be selectively targeted by inhibitors, leading to a pronounced therapeutic effect.[1] To increase therapeutic effectiveness and decrease side effects during treatment, we aimed to develop a specific targeting of leukemic cells with irreversible LSD1 inhibitors.

To achieve target-specificity, pharmacologically inactive and nontoxic forms of LSD1 inhibitor **1a** with a nitro-aromatic system, so-called *bioreductive prodrugs*, are designed, synthesized and tested against LSD1 activity *in-vitro* and on cultured AML THP1 cells. As prodrug-activating enzyme, the *E. coli* Nitroreductase NfsB (NTR) was selected, that is introduced in leukemic cells using a virus-mediated transfection. By reduction of the nitro-aryl bioreductive system by the NTR, the active tranylcypromine-based LSD1 inhibitor is subsequently released and forms a covalent adduct with the cofactor FAD leading to an irreversible inhibition of LSD1.

We identified promising prodrug/drug pairs by measuring the expression of CD86 surface marker and by performing colony-forming unit assays with THP1 cells.[2] Several prodrugs are converted into the active parent drug by the NTR, which is solely expressed in transfected tumor cells. Depending on the nitro-aryl system, different activation patterns can be observed both *in vitro* and *in vivo*. By applying different targeting techniques such as antibody-directed enzyme-prodrug therapy (ADEPT) and gene-directed enzyme-prodrug therapy (GDEPT)[3], these prodrugs provide a direction for more selective anti-cancer drugs.

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# DISCOVERY OF NEW 6-SUBSTITUTED-2(3H)-BENZOTHIAZOLONES AND 6-SUBSTITUTED-2(3H)-BENZOXAZOLONES: NOVEL σRs LIGANDS TO TREAT NEUROPATHIC PAIN

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Neuropathic pain is a chronic condition which drastically affected the quality of life of approximately 20 million adults daily in the USA [1]. Medications to treat neuropathic pain are available, but current treatments possess notable liabilities and often impair quality of life. Thus, there is still the need to develop alternative painkillers with fewer side effects. Sigma receptors (σRs) have been proposed as a promising target to treat chronic pain, due to the ability of σR to modulate analgesic responses. Our research team has been working on the design and synthesis of more selective σRs ligands. More recently, we have developed [$^{18}$F]FTC-146, a potent and selective $\sigma_1$R ligand currently under phase I clinical trials as PET/MRI diagnostic agent to pinpoint the site of peripheral nerve injury [2]. Herein, we report the design and synthesis of a new series of high-affinity $\sigma_1$R ligands with anti-neuropathic pain effects in mice. Among them, 3-(2-(azepan-1-yl)ethyl)-6-benzylbenzo[*d*]thiazol-2(3*H*)-one (**MCI 77**) and 3-(2-(azepan-1-yl)ethyl)-6-(3-fluorobenzyl)benzo[*d*]oxazol-2(3*H*)-one (**MCI 92**), exerted a dose-dependent anti-allodynic effects in both the mouse chronic constriction injury (CCI) and chemotherapy-induced peripheral neuropathy (CIPN) models of neuropathic pain after i.p. administration. Furthermore, minimal locomotor impairment and respiratory depression was observed for the tested compounds at therapeutic doses. These data support the progression of these compounds for further lead-optimization process to develop a novel neuropathic pain treatment with fewer clinical liabilities of use.

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# DISCOVERY OF NEW POTENTIAL INHIBITORS OF 14-3-3 PROTEINS IN TRYPANOSOMATID PARASITES

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Trypanosomatid parasites are responsible for some of the most important neglected tropical diseases, affecting an estimated 1 billion people around the world and collectively causing over 150 000 deaths per annum.[1] The human diseases caused by these protozoan parasites include African trypanosomiasis (HAT, also known as sleeping sickness) caused by two subspecies of *Trypanosoma brucei* (*T. brucei*); Chagas disease which is caused by infection with *Trypanosoma cruzi (T. cruzi)*; and Leishmaniasis which is caused by various subspecies of *Leishmania*. Currently, there are no vaccines for these diseases and the available drugs are far from ideal, making the need for novel drug targets and the development of new, effective drugs even more urgent. [2,3]

Our strategy aimed to "Recycling/repurposing Non-Active Compounds" (RNACs), belonging to an in-house library. These molecules were designed and synthesised toward a specific target, but due to their lack of activity, they were deprioritised as inactive compounds. An in-house library of RNACs was prepared. The research led to 80 RNACs. In order to investigate unexplored druggable chemical space against leishmaniasis and Chagas' disease, these compounds were screened phenotypically against the intracellular amastigote stage of *T. cruzi* and the intracellular form of *Leishmania donovani. [4]* A compound named KLDS47 showed significant potency against *T. cruzi* with low cytotoxicity against mammalian host cells. KLDS47 was originally developed as part of a set of molecules designed to be inhibitors of the human 14-3-3, some of them demonstrated activity. KLDS47 was inactive, nevertheless, due to the structural similarities, it was possible to consider that 14-3-3 proteins of *Trypanosoma* could be the potential target of this compound. [5,6]

A deeper investigation was carried out, and the bioactive molecule was assessed against the different stages and families of the trypanosomatid parasites, showing a notable activity against the bloodstream form of *T. brucei*.

To determine the mode of action and validate the 14-3-3 protein as the target, a set of 40 analogues of KLDS47 were designed, synthesized and assessed as potential inhibitors of 14-3-3 proteins against *T. brucei* cell lines moderately overexpressing both 14-3-3 isoforms (Tb14-3-3). Marginal shifts in the potency of 4 analogues suggest that may target may target 14-3-3 I/II heterodimeric proteins in bloodstream *T. brucei*.

Two of the compounds were used to generate 5 resistant *T. brucei* cell lines (WGS currently in analysis) while cross-resistance assays highlighted that both compounds are likely to be hitting the same target. At the same time, these compounds were screened against a genome-wide overexpression library in *T.brucei*. Preliminary results suggested that overexpression of the protein phosphatase 1 catalytic subunit (PP1 enzyme) was associated with resistance to these compounds. It is known that in humans, PPI interacts with 14-3-3ζ and regulates nuclear trafficking, it is possible that this phosphatase may have a similar function in *T. brucei*.[7] Our working hypothesis is that these new compounds may bind to the Tb14-3-3 and inhibit the interaction with PP1.

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# DISCOVERY OF NOVEL CHEMOTYPES OF COMPETITIVE AMPA RECEPTOR ANTAGONISTS AS POTENTIAL ANTI-EPILEPTIC AGENTS USING NATURAL PRODUCTS LIBRARY

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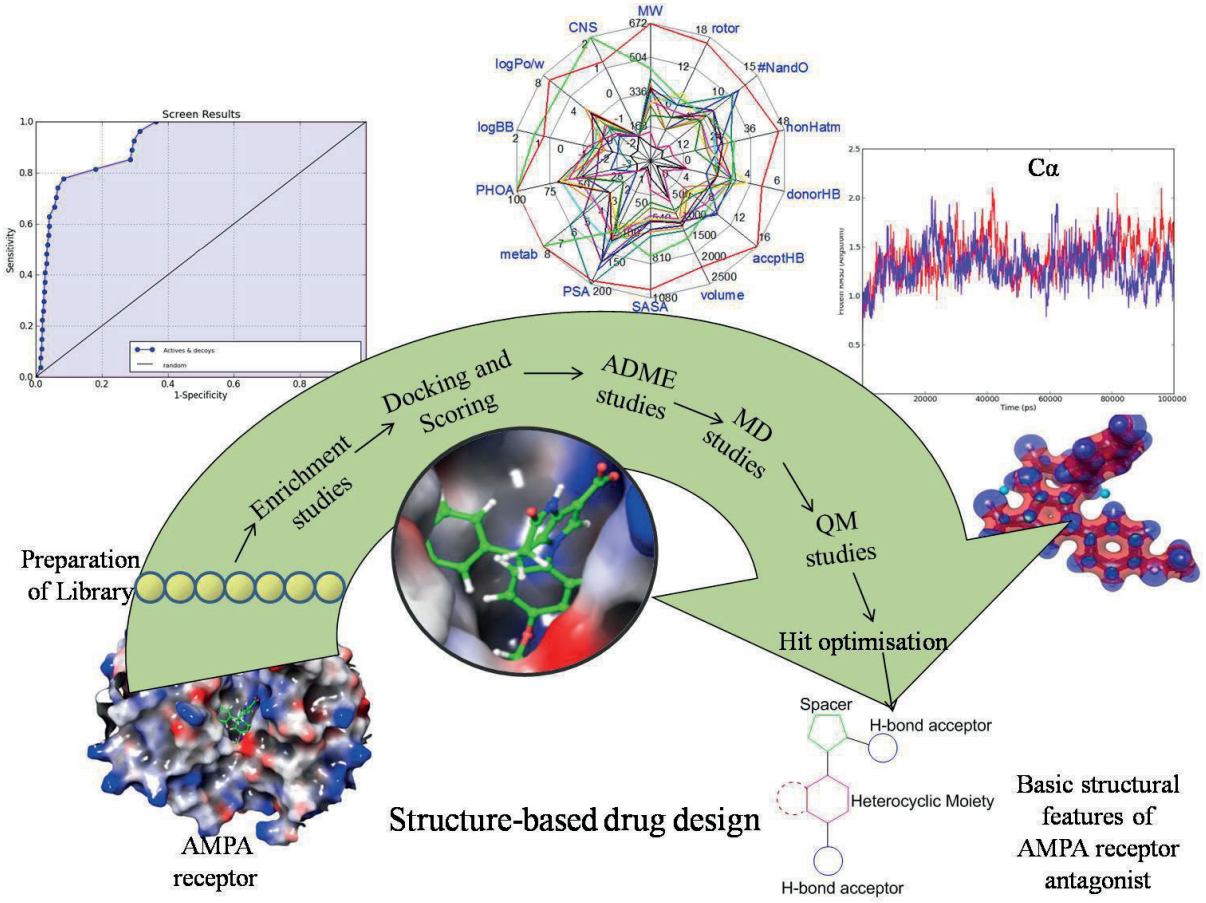
Competitive AMPA receptor antagonists serve as the promising and validated strategy towards the development of novel anti-epileptic agents (1,2). For this purpose, the structure-based virtual screening approach on library of natural compounds led to the discovery of eleven novel diverse competitive AMPA receptor antagonists with better docking and dG bind scores than the co-crystallized ligand (3). Validation of the screening protocol was accomplished at three levels like superposition, enrichment and simulation studies. Involvement of the crucial amino acid interactions such as Thr91 and Arg96 involved in the binding of the co-crystallized ligand was set as the basic criterion for selecting hits on the basis of the ligand-protein interactions. The topmost hit with best dG bind score was subjected to simulation studies, quantum mechanics and hit optimization study. Computational models developed through validated virtual screening protocol with better pharmacokinetic performance provides *in silico* evidence towards the development of better therapeutic regime of epilepsy.

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# SYNTHESIS AND BIOLOGICAL EVALUATION OF SALICYLAMIDE-BASED PSEUDOPEPTIDES WITH DIFFERENT ANTICANCER ACTIVITIES

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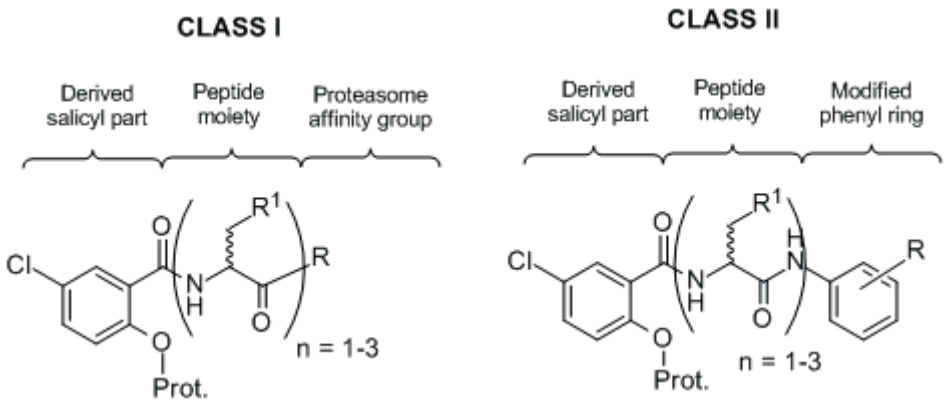
Our previous studies revealed that 2-hydroxy-N-(arylalkyl)benzamides induce potently apoptosis in cancer cell lines [1,2,3,4]. Chemically, these compounds consist of a short dipeptide or tripeptide chain bonded to O-benzyl salicylic acid on the N-terminus and carrying various functional groups on the C-terminus; therefore we designate them as pseudopeptides. The compounds can be classified into several groups with clearly distinct mechanisms of action (**Figure 1**).

Novel salicylamides (**CLASS I**) potently stabilize levels of green fluorescence protein (GFP) fused to a short degron that is rapidly degraded by a proteasome. Live-cell imaging confirmed that the compounds induce accumulation of GFP in a time- and a dose-dependent manner. In addition, biochemical analyses revealed increased levels of polyubiquitinated proteins in treated cells, indicating the proteasome as the main target of our newly prepared compounds.

Newly prepared salicylamides (**CLASS II**) bearing the combination of optically pure aminoacids, namely aromatic phenylalanine or aliphatic leucine. All compounds display antiproliferative activity in tested cancer cell lines and eight of them reach up single-digit micromolar $GI_{50}$. These salicylamides cause loss of FAK signaling and interfere with cell attachment, block proliferation and induce apoptosis in the HCT-116 cell line.




**Acknowledgement**

This research was supported by the Czech Science Foundation (GA 18-03847S), by Palacky University (IGA_PrF_2019_013) and by Faculty of Chemical Technology, University of Pardubice.

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# IDENTIFICATION OF NOVEL SMALL MOLECULES THAT CAN INDUCE DIFFERENTIATION TO ACUTE MYELOID LEUKEMIA CANCER CELLS

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Acute Myeloid Leukemia (AML) is the most aggressive type of blood cancer, characterised by a block in the differentiation of white blood cells, leading to the accumulation of abnormal and immature cells in the bone marrow. Patients with AML fail to make normal blood cells. Despite growing knowledge and understanding of the disease, treatment has remained unchanged in the last years; it usually requires two phases of intensive chemotherapy aimed at killing the AML cells, which often results in numerous side effects and low rates of complete remission (CR).[1] AML is a high unmet clinical need which urges the discovery of new treatments.

An alternative approach to the current "killing therapies" is to instead overcome the differentiation block of the AML cells, forcing them into mature blood cells. The promise of this differentiation therapy has been demonstrated by the big success of all-trans retinoic acid (ATRA), which has been shown to induce CR in 90% of patients with APL, a sub-type of AML, by enabling the maturation of the leukemic cells.[2,3] However, it is only effective in patients that carry a particular mutation, representing 10% of all AML. Therefore, our aim is to identify novel small molecules that can differentiate AML cells regardless of their mutation status, to find a therapy that is effective in all AML patients.

With this goal in mind, we have developed a robust *in vitro* screening assay which we utilised to perform a pilot screen of over 1,000 small molecules. The HTS was followed by a validation strategy which identified a range of structurally distinct hits that can differentiate AML cells of several subtypes. An extensive medicinal chemistry programme to improve the properties of these compounds has enabled the progression to *in vivo* studies. We will present for the first time the results of our *in vivo* efficacy studies, which demonstrate that our lead compounds were able to decrease tumour volume in a xenograft model of AML.

A lead optimisation campaign is currently underway, as well as mechanistic studies to shed light on the targeted pathways. So far, some preliminary RNA sequencing experiments have confirmed that AML cells exposed to our compounds possess a gene expression signature indicative of differentiation, and suggest a novel mechanism of action. Moreover, we have some evidence that our molecules are dual-targeting, affecting complementary biological processes that contribute towards the observed effect.

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# MULTI-TARGET DRUGS FOR THE TREATMENT OF SCHIZOPHRENIA – DOPAMINERGIC HYPOTHESIS AND BEYOND

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Polypharmacology is nowadays considered an increasingly crucial aspect in discovering new drugs as a number of original single-target drugs have been performing far behind expectations during the last ten years. In this scenario, multi-target drugs are a promising approach against polygenic diseases with complex pathomechanisms such as schizophrenia. Indeed, second generation or atypical antipsychotics target a number of aminergic G protein-coupled receptors (GPCRs) simultaneously. Novel strategies in drug design and discovery against schizophrenia focus on targets beyond the dopaminergic hypothesis of the disease and even beyond the monoamine GPCRs. In particular these approaches concern proteins involved in glutamatergic and cholinergic neurotransmission, challenging the concept of antipsychotic activity without dopamine $D_2$ receptor involvement [1].

As a part of our research on CNS agents we performed structure-based virtual screening to identify multi-target ligands of aminergic G protein-coupled receptors with affinity to different dopamine and serotonin receptors [2]. As a result we identified 10 active compounds, confirmed their affinity *in vitro* and four of them (D2AAK1, D2AAK2, D2AAK3 and D2AAK4) were studied as potential antipsychotics [3].

Here we present preliminary *in silico* studies of these four compounds and their selected derivatives in order to identify molecular targets responsible for their antipsychotic, pro-cognitive and anxiolytic activity beyond the dopamine and serotonin receptors. First we studied these compounds using PASS and Pharma Expert software which are widely applied tools for bioactivity prediction, target fishing and drug repositioning. Next, we used molecular docking and molecular dynamics to study findings from PASS and Pharma Expert at the molecular level. The most interesting results will be verified experimentally followed by the optimization of our lead structures concerning their affinity to the identified molecular targets.

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# IMPACT OF TOPOLOGY OF MORPHOLINE 5-ARYLIDENEIMIDAZOLONE DERIVATIVES ON ABILITY TO BLOCK BACTERIAL RESISTANCE MECHANISMS

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Nowadays, bacterial multidrug resistance (MDR) is a serious problem in every country. Possibilities to overcome MDR strains include both, synthesis of new antibacterial drugs and searching for antibiotics "adjuvants". The second option concerns compounds able to block at least one mechanism of resistance, *e.g.* efflux pumps, without intrinsic antibacterial activity. Our previous studies among arylideneimidazolones proved their activity as potential antibiotic adjuvants[1]. Furthermore, morpholine is the amine present in potent bacterial efflux pump inhibitors (EPIs), i.e. **MBX2319**[2] and **BG1167**[3]. In this context, a group of 11 new morpholine derivatives of 5-arylideneimidazolone (**1**-**11**, Fig.1) was designed based on both, structural similarities to previous active adjuvants and *in silico* ADMET filters.

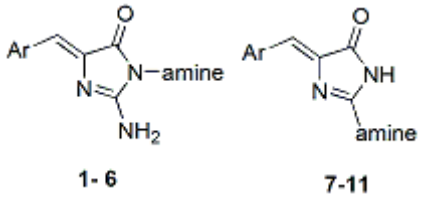


Fig. 1 General structures of amine-5-arylideneimidazolones.

The new compounds were synthesized within 3-4 step synthetic pathway, including: (i) Knoevenagel condensation, (ii) S-methylation, (iii) reaction with amine. In case of synthesis with primary amine, Dimroth rearrangement was observed. Final products were tested for their antibiotic adjuvant properties in Gram negative pathogens (*E.aerogenes* and *E.coli*), using microdilution tests. EPI properties of selected compounds were examined in Real-Time Efflux (RTE) assays. The most active compound significantly increased efficacy of different antibiotics in the MDR *E.coli* strain. None of tested compounds were able to affect concentration of antibiotics in *E.aerogenes* strains in the microdilution tests. Additionally, the 5-arylidenoimidazolones tested effectively blocked AcrAB-TolC efflux pump during RTE assays performed in both, *E.aerogenes* and *E.coli strains,* over-producing the pump. Based on the obtained results, morpholine connected by propyl linker with 3-position of imidazolone as well as fluorene moiety at position 5 seem to be beneficial for the activity considered.

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# NOVEL ACRIDINE DERIVATIVES AS TYROSYL-DNA PHOSPHODIESTERASE 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 inhibition of DNA repair enzymes can induce DNA damage leading to cell death. 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-DNA complexes. 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 these 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 the early results showed, in accordance with *In Silico* calculations, that the second basic side chain is essential for this activity. Addittionally, crucial is the precence of methoxy substitution at the 7 position of the aza-acridine core.

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# A CHEMICAL PROBE FOR TIGAR

**Steven T. Kay (1), Blair Johnston (2), Simon Mackay (2), Louise Young (2), Ming Yang (3), Karen Vousden (3), Nicholas C. O. Tomkinson (1)**

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TIGAR (Tp53-Induced Apoptosis and Glycolysis Regulator) is a phosphatase enzyme which alters the flow of metabolites along two connected pathways: glycolysis and both the oxidative- and non-oxidative- branches of the pentose phosphate pathway (PPP). TIGAR overexpression has been observed in several cancers (e.g. breast and intestinal cancer) and is believed to aid DNA repair (nucleotide synthesis) and protect the cell from oxidatively induced apoptosis (depletion of ROS species).[1,2] This identified TIGAR as a potential therapeutic target for several disease types.

A chemical tool has been developed for the emerging oncology target TIGAR, which is currently being evaluated in a cellular environment, in the laboratories of Professor Karen Vousden. Using molecular modelling, we designed and synthesised a series of diverse molecular scaffolds which resulted in the identification of a novel hit series to inhibit the target. Upon hit identification, an SAR study was undertaken to interrogate the active site of TIGAR with the aim of driving potency and selectivity towards this target. This poster will describe the synthesis and biological evaluation of a novel lead compound for TIGAR.

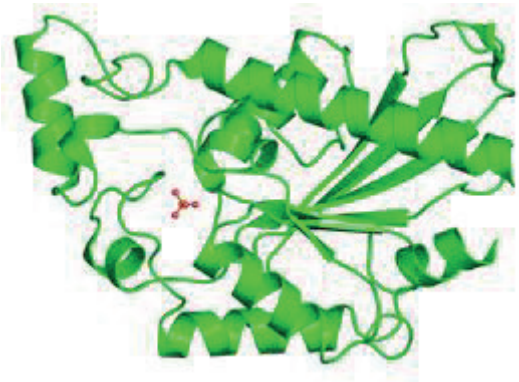

**Figure 1:** *TIGAR protein structure with phosphate ion bound in active site.*

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# GEOMETRIC ISOMERS OF STYRILPIPERIDINE DISCRIMINATE BETWEEN MONOAMINE OXIDASE ISOFORMS A AND B

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Flavin-dependent oxidoreductases monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) are important targets in the therapy of neurological disorders such as depression and Parkinson's disease.[1,2] As a part of our screening program devoted to discovery of novel compounds targeting neurodegenerative diseases, *trans* -styrilpiperidine **1** (Figure 1A) was identified as a selective human (h)MAO-B inhibitor. Interestingly, its *cis* isomer selectively inhibited human (h)MAO-A. The selectivity was explained by molecular modelling studies. This distinct activity of geometric isomer pair prompted us to study the structure-activity relationships (SARs) by constructing a focused library of diversely substituted piperidines. Interestingly, 1,4-disubstituted *N*-propargylstyrilpiperidines with *trans* vinyl linker connecting piperidine and benzene ring irreversibly inhibit hMAO-B with low nanomolar $IC_{50}$ values. On the other hand, *cis* isomers with small substituents on the benzene ring irreversibly inhibit human (h)MAO-A with high selectivity over hMAO-B (Figure 1A). Crystal structures of 4 *N*-propargylstyrilpiperidines in complex with human MAO-B were resolved, confirming irreversible covalent modification of FAD cofactor (Figure 1B).

Compounds are not cytotoxic to neuroblastoma SH-SY5Y cell line ($EC_{50}$ > 100 μM) and show neuroprotective properties in 6-hydroxydopamine cell-based model of Parkinson's disease. They also display favorable *in-vitro* pharmacokinetic parameters in terms of oral bioavailability and BBB permeability. *Ex-vivo* experiments further on demonstrate MAO-A and MAO-B inhibition after *i.p.* and also *per oral* administration in mice brain homogenates. Importantly, selective hMAO-A inhibitor **3** (Figure 1A) shows antidepressant activity in mice after *i.p.* administration (0.3 mg/kg) in chronic 10-day treatment regime.

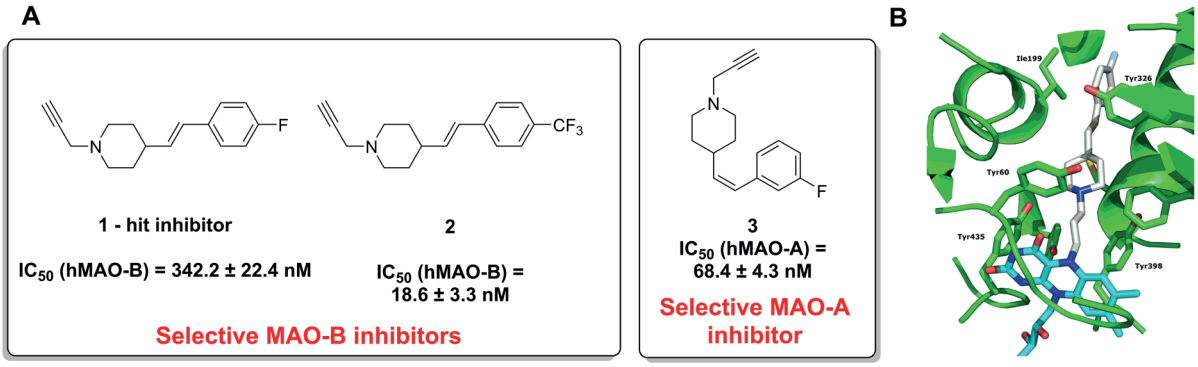


**Figure 1:** Development of styrilpiperidines as *selective MAO-A and MAO-B inhibitors.*

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# CAVER WEB: ANALYSIS OF PROTEIN TUNNELS AND LIGAND BINDING TRAJECTORIES IN DRUG DESIGN

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**Objectives**: Protein tunnels and gates are attractive targets for drug design [1]. Tunnels are important for the transport of ligands, solvent and ions, and can be found in many enzymes, ion channels and membrane proteins. Here, we wanted to create a user-friendly web tool to analyse the tunnels and channels of proteins, and the transport of ligands through these pathways.

**Methods**: Caver Web 1.0 uses the Caver 3.02 [2] for tunnel detection and the new CaverDock 1.0 [3,4] for ligand transport analysis. CaverDock is a fast, robust and accurate tool, which allows the screening of binding and unbinding processes for pharmacologically interesting compounds. It is based on a heavily modified AutoDock Vina algorithms [5] and we have previously successfully tested it with many pharmaceutically interesting targets, such as cytochrome P450 17A1 and leukotriene A4 hydrolase/aminopeptidase [6].

**Results**: The identified tunnels, their properties, energy profiles and trajectories for the passage of ligands can be calculated and visualized using the Caver Web tool. The calculation of tunnels takes only 1-2 min for a single protein structure. The ligand transport analysis takes generally 2-20 min per one ligand-tunnel pair and thus the tool is applicable even for virtual screening purposes. The three tutorials presented on the web page describe three different use cases: (i) comparing tunnels of a family of enzymes, (ii) comparing the passage of a single ligand through multiple tunnels and (iii) comparing the passage of different ligands through a single tunnel.

**Conclusions:** The simple setup and graphical user interface make the tool accessible for all users who are interested in tunnel or channel identification and ligand binding analysis. Caver Web is freely available at https://loschmidt.chemi.muni.cz/caverweb.

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# MAPPING THE ORTHOSTERIC BINDING AREA OF 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 and the non-selective NECA 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 IB-MECA and NECA 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. A very good correlation was obtained betwween calculated binding free energies and esperimental activities.

ACKNOWLEDGEMENT. The author thanks Special Account for Research Grants and National and Kapodistrian University of Athens for funding to attend the Symposiun

# TARGETING OREXIN RECEPTOR TYPE 2 IN THE TREATMENT OF NARCOLEPSY

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Narcolepsy is a chronic neurologic disorder characterized by excessive daytime sleepiness and other symptoms such as cataplexy, vivid hallucinations and paralysis.(1) Narcolepsy is considered as the rare disease affecting approximately 1 in 3000 people.(2) It is believed that narcolepsy is based on autoimmune response mediated by loss of a specific hypothalamic neuropeptide, orexin (also called hypocretin).(3,4) Two orexins have been described – orexin A and orexin B. Accordingly, there are two specific receptors for the orexin peptides, orexin receptor tape 1 (OX1R) and orexin receptor type 2 (OX2R). However, patients with narcolepsy are currently treated only symptomatically. Compounds such as modafinil (non-amphetamine wake promoting compound for excessive daytime sleepiness) and sodium oxybate (short-acting sedative for fragmented nighttime sleep and cataplexy) are preferentially used.(1) An alternative to the symptomatic treatment of narcolepsy with cataplexy would be a direct orexigenic system-targeted therapy in the form of non-peptide small-molecule orexin agonists able to cross the blood brain barrier.

The aim of this work was to design, synthetize and biologically evaluate a novel class of the orexin receptor 2 type agonists. From the group of proposed novel structures, we selected those that fulfill several criteria including CNS multiparameter optimization desirability with predicted proper interaction with OX2R as shown by *in silico* methods.(5,6) Solubility profile was also one considered as one of the key parameters with logS values higher than -4. Within our contribution, all the achieved results in syntheses and biological evaluations of prepared derivatives will be presented.

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# IN VITRO AND IN VIVO STUDIES OF NEW LIGANDS OF AMINERGIC GPCR RECEPTORS

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G protein-coupled receptors (GPCRs) are an important target for drugs in neuropsychiatric disorders such as schizophrenia, Parkinson's disease or depression. These receptors are involved in neurotransmission and participate in a wide variety of cellular processes that can be disrupted in neuropsychiatric diseases.

In the search for novel antipsychotics and antidepressants, structure-based virtual screening was performed to identify multi-target ligands of aminergic GPCR receptors. The best compounds were subjected to *in vitro* and *in vivo* studies.

Here were present cytotoxicity determination, real time proliferation measurement using the HT-22 cell line, as well as studies of the effect of a given compound on mobility, anxiety processes and depression processes carried out using mouse models.

One of the studied compounds with antipsychotic potential increased hippocampal cell division (HT-22). In addition, studies of the anxiolytic activity of this compound showed that the strongest anxiolytic effect occurs at a dose of 25mg / kg and 100 mg / kg after 45 and 60 minutes after administration of the compound. It has also been shown that the compound has no antidepressant activity at the doses tested.

The studied compound seems promising as a pharmacological tool or potential drug and will be subjected to further investigation.

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# STUDY ON THE EFFECT OF STATINS AND ANALOGUES OF SUBSTRATE ON THE CATALYTIC ACTIVITY OF SHORT AND LONG TYPE OF ADENYLATE KINASES

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Adenylate kinases (AK) catalyze the reversible reaction of the phosphate transfer between adenine nucleotides. These enzymes participate in many biological processes, such as cell differentiation, proliferation, apoptosis, cytokine secretion and adaptation to hypoxia and oxidative stress [1,2]. There are no literature reports on the adenylate kinase activators, while the only known AK inhibitors are the dinucleotide polyphosphates such as $Ap_5A$, $Ap_4A$, $Ap_6A$ and $1,N^6$-etheno-$Ap_5A$ [3,4]. Therefore there is a need to search for new AK modulators, both inhibitors and activators. By analyzing the literature reports we have found a relation between the length of the adenylate kinase LID domain and the level of their inhibition by P1,P5-diadenosine-5'pentaphosphate ($Ap_5A$). So far, the non-hydrolysable analogues of ADP and ATP were investigated as inhibitors of NTPDases [5,6] but there are no literature reports on their effect on the activity of adenylate kinases. Since the catalytic centers of two selected enzymes (hAK1, AKst) reveal a high similarity, we suppose that the different structure of the LID domain is responsible for the reported differences in the inhibitor efficiency.

Our studies confirm a different sensitivity of short and long type AKs to $Ap_5A$. The AK from *G. stearothermophilus* (long type) is inhibited by 10μM Ap5A at 54%, whereas 10μM Ap5A caused ≥96% *inhibition of* hAK1 (short type). We observed a similar trend in the AK sensitivity using the substrate analogues. For our experiments we have selected two commercially available analogues of ADP (ADP-β-S, AMP-CP) and two analogues of ATP (AMP-PNP, ADP-CP). ADP analogues (ADP-β-S and AMP-CP) caused the increase in the hAK1 activity whereas ATP analogues (AMP-PNP and ADP-CP) inhibited hAK1. Activity tests for AKst have not shown any significant effects relative as compared to the control. The obtained results revealed that these analogues affected the kinase activity in a different manner, what might be associated to the differences in the AK structure, in particular the different length of the LID domain.

Adenylate kinase participates in the control of HDL cholesterol endocytosis by liver cells [7]. In cardiology, the drugs used for lowering the blood cholesterol level are statins. Our research indicated for the first time that statins efficiently inhibit human adenylate kinase (hAK1, short type) while do not change significantly the activity of bacteria adenylate kinase (AKst, long type). Statins structure differs from the AK substrates, but their common β-hydroxy acid moiety might mimic the binding interactions of the AK substrate phosphates. Therefore, it is interesting to determine if the additional protective effect of statins used in the therapy of the circulatory system might be related to the regulation of activity and function of adenylate kinases. We have tested four statins: simvastatin (SVS), rosuvastatin (RVS), fluvastatin (FVS), and pravastatin (PVS). The hAK1 was inhibited by all tested compounds, and the largest effect was found for SVS. However, for all statins no inhibition of AKst was observed.

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# NOVEL ANNELATED XANTHINE DERIVATIVES ACTING ON ADENOSINE RECEPTORS AND MONOAMINE OXIDASE B

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According to WHO, the human population is ageing [1]. As a result of this process, an increase in the occurrence of neurodegenerative diseases such as e.g.: Alzheimer's disease is observed. The basis of these diseases is gradual and irreversible, progressive degradation of neurons, leading among others to significantly reduced ability of the human body to maintain homeostasis in response to adverse environmental factors. Unfortunately, no clear treatment strategies for Alzheimer disease have so far been developed due to the lack of full knowledge of their pathogenesis. Therefore, the search for compounds showing at the same time a high efficacy in therapy with low risk of possible side effects is being carried out. One of such broadly explored pharmacological pathways recently, is combined usage of inhibitory effects on the MAO-B along with antagonism to adenosine $A_{2A}$ receptors.

Therefore, in this study, based on our previous results [2], novel annelated xanthine derivatives were designed as dual-target-directed ligands combining $A_{2A}$ adenosine receptor (AR) antagonistic activity with blockade of monoamine oxidase B (MAO-B). A library of novel compounds was synthesized and biologically evaluated in radioligand binding studies at AR subtypes and for their ability to inhibit MAO-B. Analysis of structure-activity relationships was complemented by molecular docking studies based on previously published X-ray structures of the protein targets. The new, active annelated xanthine ligands, acting as dual target drugs may provide symptomatic relief as well as disease-modifying effects for neurodegenerative diseases such as Parkinson's disease.

**Acknowledgements**

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*K.J. Kuder & M. Zaluski contributed equally

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# POLYPHARMACOLOGY IN ALZHEIMER'S DISEASE: INNOVATIVE MTDLS COMBINING 5-HT4R AGONISM AND PROMISING IN CELLULO ANTIOXIDANT ACTIVITIES

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In a world where life expectancy is increasing, Alzheimer disease (AD) is the main cause of dementia, and touch approximatively 17% of people who are more than 75 years in France. This is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. Despite the fact that the physiopathology of AD is not entirely known at the time, some molecular causes were found such as the ß-amyloid peptides aggregation, tau-dependent neurofibrillary tangles, as well as oxidative stress and neuroinflammation. Currently, treatments available for patients are mainly acetylcholine esterase (AChE) inhibitor, which only have symptomatic benefits and do not cure AD. Then there is still a strong medical need in the AD population.

In this context, the concept of Multi-Target Directed Ligands (MTDLs) was applied to design a drug with several therapeutic targets. The envisaged MTDL should be able in first hand, to limit the development of ß-amyloid plaques obtained by the aggregation of ß-amyloid peptides (Aß). Indeed, our compounds are designed to promote the cleavage of amyloid protein precursor (APP) by α -secretase activation in order to produce a neuroprotective and soluble peptide sAPPα. This is the role of the 5HT$_4$R agonists (blue part – fig 1.) which are already studied in the CERMNin other MTDL projects and led to the discovery of Donecopride.[1]

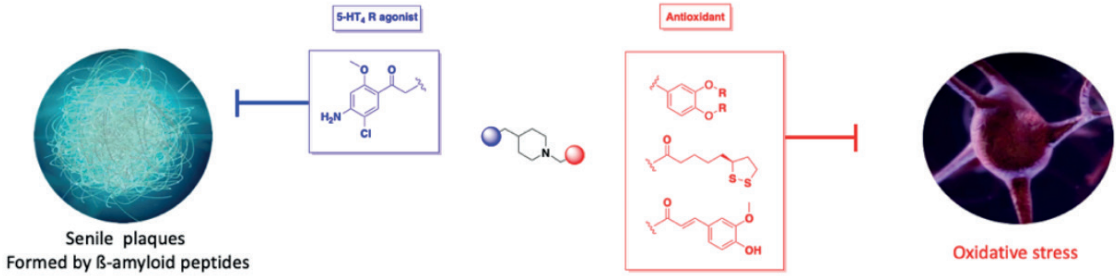


Figure 1. Targeted structure, with 5-HT$_4$R agonist moiety in blue and antioxidant moieties in red.

In another hand, it appears that the oxidative stress plays a central role in AD.[2] Adding antioxidant moiety such as polyphenol, lipoic and ferulic acid (red part- fig 1.) could trap free radicals or reactive oxygen species (ROS) and also have a neuroprotective effect. This aspect has been widely studied in Prof. Maria-Laura Bolognesi's laboratory over the years.[3] To that end, different compounds will be designed and synthesized, with both the expertise of CERMN and Prof Maria-Laura Bolognesi, in order to evaluate their s*in vitro/in vivo* properties regarding their agonist activity on 5-HT$_4$R and antioxidant properties. The development and promising *in vitro / in cellulo* results of the chloroaniline's moiety line will be described in this presentation.

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# AZEPANYLHEXYLOXY DERIVATIVES - HISTAMINE H3 RECEPTOR AFFINITY, CHOLINESTERASES INHIBITORY ACTIVITY AND ADME/TOX PREDICTION

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An azepane moiety is present in numerous biologically active molecules showing a variety of pharmacological properties.[1] Previously, we described histamine $H_3$ receptor ($H_3Rs$) antagonists with the azepane ring showing promising cholinesterases (ChEs) inhibitory activity.[2,3] Combination of ChEs inhibition with $H_3Rs$ antagonism in a single molecule might lead to multi-targeting ligands with potentially synergistic effects improving cognitive deficits in Alzheimer's Disease.

The aim of this study was to evaluate the ability of azepanylhexyloxy derivatives (general structure in **Fig. 1**) to inhibit ChEs. The compounds showing good to moderate $H_3R$ affinities (18 nM < $K_i$ < 530 nM), tested at recombinant human $H_3Rs$ stably expressed in HEK-239 cells, were chosen for further studies. These compounds were screened for ChEs using the method established by Ellman et al.[4] and demonstrated micromolar inhibition of acetylcholinesterase ($IC_{50}$ > 1.5 μM) and submicromolar inhibition of butyrylcholinesterase ($IC_{50}$ > 0.16 μM). Moreover, ADME/Tox properties of tested compounds were calculated using the free web tools (SwissADME and ProTox-II).[5,6]

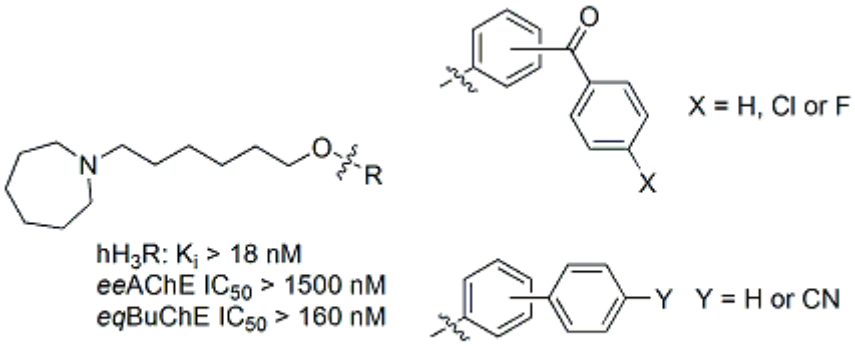


Fig.1. General strucutre of tested compounds

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# OPTIMIZATION OF KINASE INHIBITION AND METABOLIC STABILITY OF PYRAZOLOPYRIDINE INHIBITOR OF YEAST KINASE YCK2

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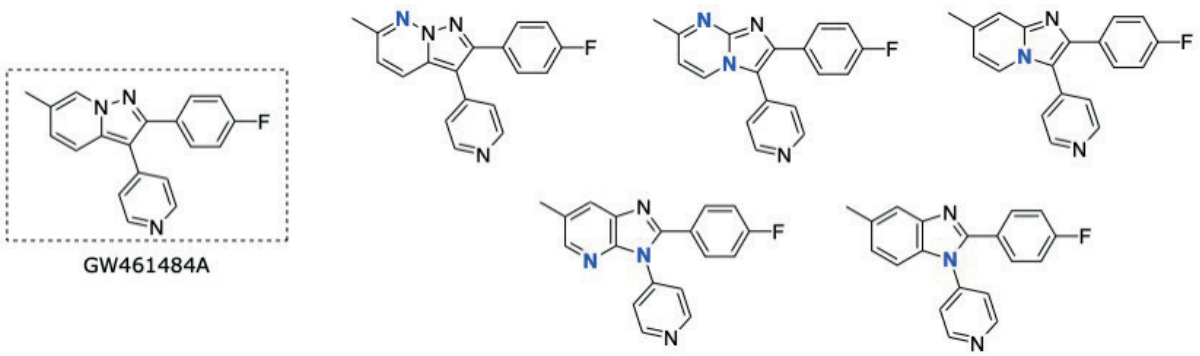
The fungus Candida albicans is a leading cause of nosocomial infections, with mortality rates often exceeding 40% despite treatment.[1] Emerging resistance to existing therapies necessitates the identification of new antifungal mechanisms and the development of new antifungal drugs.[2] Towards this aim we screened the first and second generation Published Kinase Inhibitor Set (PKIS)[3,4]against caspofungin-resistant C. albicans strains. We identified pyrazolopyridimidines that had both single-agent activity and the ability to potentiate the effects of caspofungin. The lead compound GW461484A exhibited 85% growth inhibition in combination with caspofungin relative to caspofungin as a single agent control. However, GW461484A was revealed to have several limitations. First, the compound was rapidly metabolized in liver S9 fractions, potentially due to oxidation of its electron-rich ring system. Secondly, while GW461484 had high activity, the lack of complete inhibition may allow for resistance mechanisms to develop. We sought to address these two issues with a program of iterative medicinal chemistry. We now describe our medicinal chemistry program to improve metabolic stability and increase activity.

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# DESIGN AND SYNTHESIS OF NOVEL SMALL MOLECULE AGONISTS OF THE FPR2 RECEPTOR AND THEIR POTENTIAL APPLICATION IN THE TREATMENT OF CARDIOVASCULAR INFLAMMATION

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The resolution of inflammation (RoI) represents a new way to treat cardiovascular inflammatory pathologies. Formyl peptide receptor 2 (FPR2) is a member of the G-protein coupled receptor family and expressed mainly by mammalian phagocytic leukocytes. FPR2 is involved in the RoI process with implications in several cardiovascular inflammation processes. The development of new small molecule FPR2 agonists which can empower an endogenous pro-resolving pathway might be a breakthrough in the treatment of cardiovascular diseases.

A range of known small molecule FPR2 agonists was initially investigated using homology modelling, molecular docking and generation of a pharmacophore hypothesis. Based on this we proposed a binding site with three hydrophobic subpockets and two polar clusters. For each molecule, important aromatic stacking with at least one of the amino residues: Phe257, Phe292, Phe163, Tyr175 and His102 was observed. As a next step, we sought to design novel agonists and the first approach employed was to use the knowledge gained from SAR studies to find alternative bioisosteric replacements. The second approach employed in the design of novel agonists was screening the GLASS (GPCR-Ligand Association) database using our pharmacophore model using Phase Ligand Screening. A new series of agonists was then synthesized and screened for their ability to activate $Ca^{2+}$ mobilization and β-arrestin recruitment. The compounds showed the ability to activate the FPR2 receptor in the nanomolar range in both assays and they have promising *in vitro* ADMET profiles. Finally, using static adhesion and flow chamber adhesion assays we have shown that FPR2 agonists can reduce the number of adherent neutrophils which indicates their anti-inflammatory and pro-resolving properties. Based on the results from the primary cell assays and in-house *in vitro* tests, we have chosen two compounds for further optimization which is currently in progress.

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# MODULATION OF HUMAN NEUTROPHILS' OXIDATIVE BURST BY 2'-HYDROXYCHALCONE DERIVATIVES

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Hypochlorous acid (HOCl) is considered one of the most relevant reactive oxygen species (ROS) in pathogens elimination and the most bactericidal oxidant known to be produced by neutrophils. The infiltration of activated neutrophils at inflammation sites is a very common feature of many debilitating diseases. During inflammation, neutrophils undergo a process designated as oxidative burst during which HOCl may be sustainably overproduced and cause deleterious effects on the surrounding tissues [1].

Chalcones are heterocyclic compounds of natural origin, considered as a class of open chain flavonoids with the 1,3-diaryl-2-propen-1-one molecular pattern (Fig.1). The chalcone family has an extensive structural diversity and their chemistry continues to be of interest within the scientific community due to its recognized biological activities, from which the anti-inflammatory activity stands out [2]. Thus, the development of new anti-inflammatory drugs based on chalcones scaffolds with oxidative burst inhibitory property and HOCl scavenging activity may be new therapeutic promises in inflammation control.

The aims of the present study were to investigate the ability of 2'-hydroxychalcones substituted at *para*-position (Fig. 1) to modulate human neutrophils' oxidative burst and to further scrutinise if they were able to scavenge HOCl, establishing the respective substituent group relevance on their activity.

Chemiluminescent detection was used to investigate the oxidative burst modulation by the studied chalcones. For this purpose, human neutrophils were isolated and stimulated with phorbol 12-myristate-13-acetate and the produced ROS were detected using luminol as probe [3]. Fluorimetric detection was used to measure the ability of the studied chalcones to scavenge HOCl and consequently inhibit the oxidation of the non-fluorescent probe dihydrorhodamine 123 (DHR) to the fluorescent rhodamine [4].

In general, the obtained results for the studied 2'-hydroxychalcones indicate that the substitution at *para*-position of the aromatic B ring favours both the modulation of human neutrophils' oxidative burst and the scavenging of HOCl. However, in the modulation of neutrophils' oxidative burst studies it was possible to note that the presence of the methoxyl group (Fig.1, chalcone 2) significantly decreased the chalcone activity, when compared with other substituent groups. The most promising chalcone found was chalcone 3. This chalcone was the most potent scavenger of HOCl and one of the most actives in the inhibition of neutrophils' oxidative burst, highlighting the importance of a *p*-OH group in B ring.

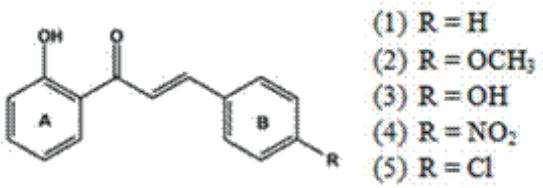


**Fig.1.** Chemical structure of the studied 2'-hydroxychalcones.

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# ELUCIDATION OF THE MECHANISM OF ACTION FOR BENZIMIDAZOLE ANALOGUES AS POTENT KYNURENINE PRODUCTION INHIBITOR

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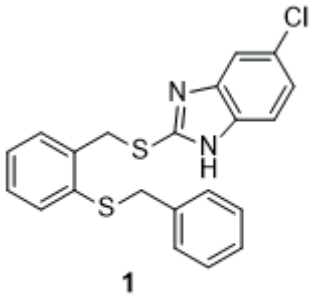
Kynurenine and its metabolites are responsible for immunological tolerance. It has been reported that kynurenine modulates T cells by suppressing their proliferation and inducing apoptosis, and it also activates regulatory T ($T_{reg}$) cells. These effects influence the pathology of autoimmune diseases and, in particular, cancer immune tolerance. Furthermore, kynurenine has been identified as an endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor (AhR). Cancer-cell-derived kynurenine promotes tumour-cell survival and motility and suppresses the antitumour immune response through AhR in an autocrine/paracrine manner. With progress in understanding cancer immunology, disruption of the PD-1/PD-L1 immune checkpoint successfully led to the new cancer therapies nivolumab and pembrolizumab. Consequently, the abrogation of kynurenine production in cancer cells is considered a promising approach to anticancer therapy.

The importance of the kynurenine in drug discovery has prompted efforts to identify the modulators. We found that compound **1** exhibits potent inhibition of cellular kynurenine production ($IC_{50}$ = 0.34 μM) despite its unexpectedly minor effect on the enzymatic activity of recombinant human indoleamine 2,3-dioxygenase (IDO), which is the regulatory enzyme for producing kynurenine. Analysis of the mechanism of action revealed that compound **1**suppresses IDO expression at the protein level by inhibiting STAT1 expression in IFN-γ-treated A431 cells. In this presentation, we report the synthesis and the biological activities of compound **1**.




**1**

$IC_{50}$ > 100μM (IDO)
$IC_{50}$ = 0.46μM (A431)

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# INHIBITION OF THE DHHC SUPERFAMILY

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The DHHC (Asp-His-His-Cys) palmitoyltransferases are a family of 24 eukaryotic integral membrane enzymes that catalyse the reversible attachment of fatty acids onto cysteine residues. The roles of S-acylation are varied, including regulating membrane attachment, mediating intracellular trafficking and modulating protein stability, and the number of S-acylated proteins is in the several thousands.[1] Studies have shown that individual DHHC enzymes are crucial for normal physiological function, with several being linked to prominent disease states. This is especially prevalent with cancers and neuropsychiatric disorders, for which the chemical toolbox available to study this exciting enzyme family remains extremely limited.

Our collaborators, have established the first selectivity profiles for the DHHC superfamily, specifically between two structurally similar DHHCs, 3 and 7.[2] Chemical tools have been developed in order to further elucidate these selectivity profiles, and provide a selective inhibitor for each of these enzymes. Using a structure-based approach, several series of compounds were designed, synthesised and biologically evaluated in a cellular environment. Work on this project has led to the development of two novel inhibitors for the DHHC superfamily.

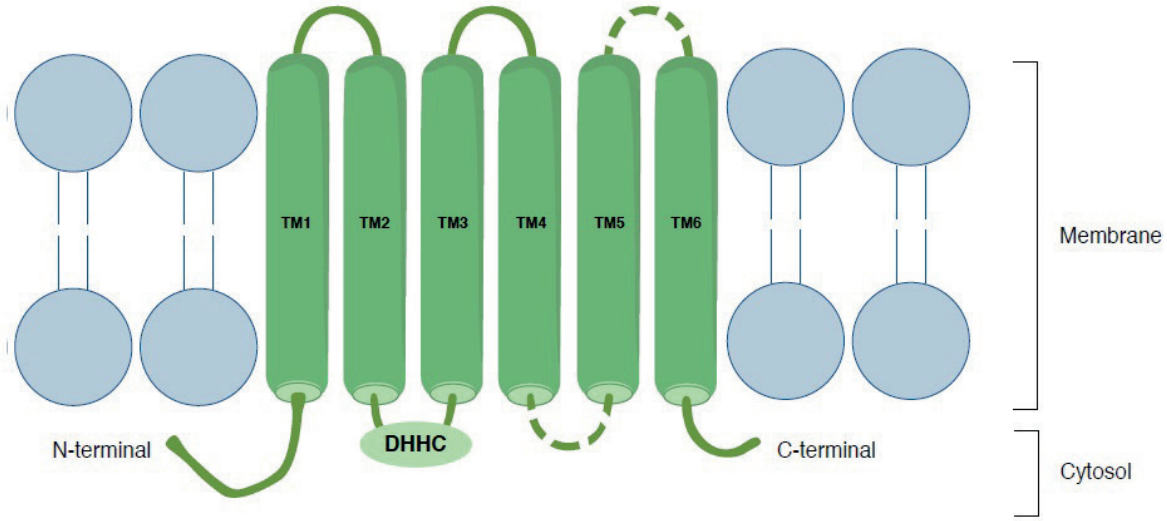


**Figure 1: Topology of the DHHC superfamily.**

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# BENZO[D]THIAZOL-2(3H)-ONES AS NEW POTENT SELECTIVE CB2 AGONISTS WITH ANTI-INFLAMMATORY PROPERTIES

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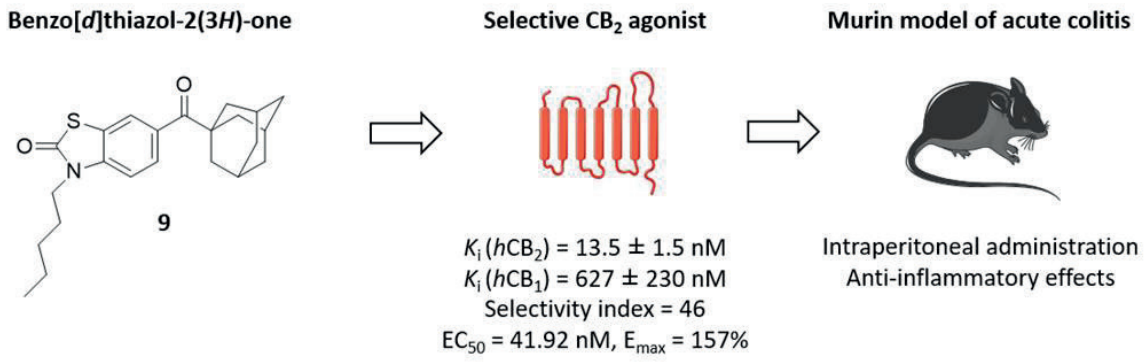
The high distribution of $CB_2$ receptors in immune cells [1] suggests their important role in the control of inflammation [2]. $CB_2$ selective agonists have the capability to modulate inflammation without triggering psychotropic effects due to the activation of $CB_1$ receptors [3-4]. Therefore, there is a growing evidence to consider this receptor as an attractive therapeutic target. More specifically, $CB_2$ receptors activation represents a very promising strategy to treat gastrointestinal inflammatory diseases.

In this work, we designed new selective $CB_2$ agonists based on a 2-oxo-2,3-dihydro-1,3-benzothiazolinone scaffold. Structure-activity relationships were studied from a series of 22 compounds. From these pharmacomodulations, we identified the importance of having both a bulky aliphatic group attached to the ketone at position 6 and an alkyl chain at *N*3-position of the heterocycle. This drug design project led to the discovery of a very potent and selective $CB_2$ agonist in the nanomolar range able to counteract colon inflammation in vivo.

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# SYNTHESIS OF NOVEL PHARMACEUTICALLY-RELEVANT FLUORINATED AMINES

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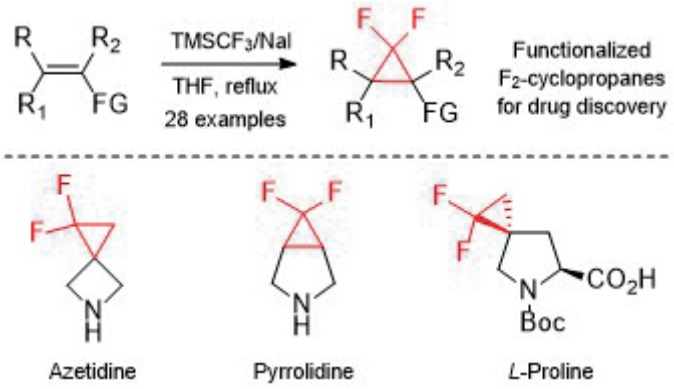
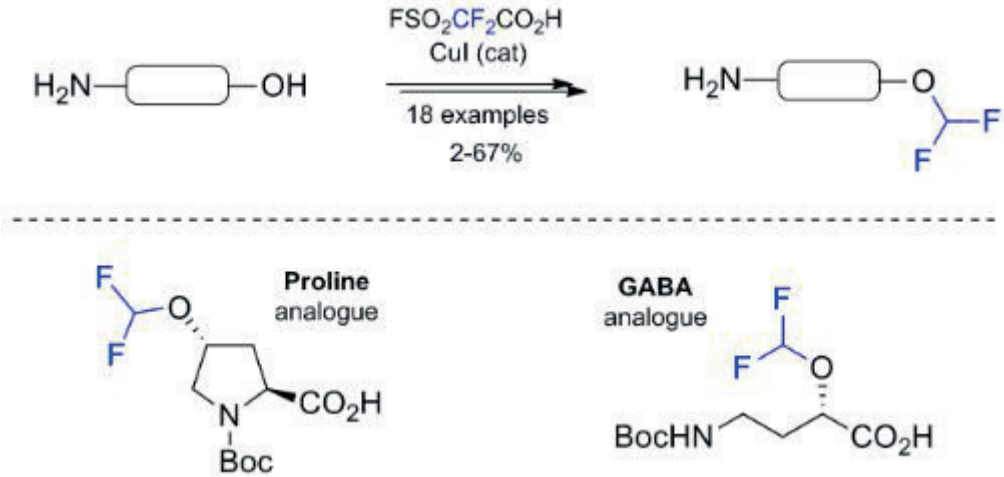
Modern drug discovery is hard to imagine without fluorine: ca. 20% of all pharmaceuticals contain this element. To date, however, only a tiny part of the theoretically possible building block structures are synthesized. Many simple combinations of fluorine with carbon and nitrogen atoms are still unknown.

Commercially accessible fluorinated alicyclic amines are mostly limited to pyrrolidines and piperidines. The latter are quite popular in medicinal chemistry. In this work, we synthesized a library of novel aliphatic saturated amines.[1,2] Details of their design and synthesis will be reported.




**Scheme 1.** Synthesis of functionalized difluorocyclopropanes: unique building blocks for drug discovery.




**Scheme 2.** Cu-catalyzed O-difluoromethylation of functionalized aliphatic alcohols: an access to complex molecules with $OCF_2H$ group.

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# DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF N-(PYRIDINYL)BENZAMIDES AND N-(PYRIDINYL)-2-PHENYLACETAMIDES AS POTENTIAL ANTIMYCOBACTERIAL AGENTS

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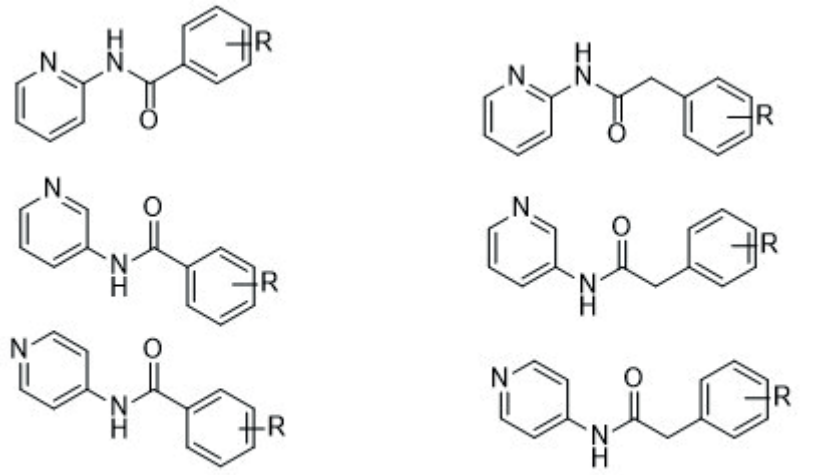
Tuberculosis is the leading cause of death worldwide among infectious diseases[1]. It is caused by *Mycobacterium tuberculosis* and can be treated with first-line anti-TB drugs, however due to increasing prevalence of antimicrobial resistance it becomes more difficult to overcome the disease with already available medicaments. *N*-(pyridinyl)benzamides (**1**) and *N*-(pyridinyl)-2-phenylacetamides (**2**) derivatives presented on the poster have been synthesized by reacting different aminopyridines with selected derivatives of benzoyl chloride or 2-phentylacetyl chloride. All compounds were tested for biological activity against selected strains of *Mycobacterium* (*M. tuberculosis* H37Rv, *M. kansasii*, *M. avium*, *M. smegmatis)* and selected fungal and bacterial strains. The series is based on previously published isosteric series of *N*-(pyrazin-2-yl)benzamides[2]. The minimum inhibitory concentration (MIC) for tested mycobacterial strains was determined for all tested compounds beside isoniazid as a reference standard drug. Results of the biological testing and structure activity relationships are discussed in the poster.



**1** R=Selection of substituents

**2** R=Selection of substituents

*This work was supported by the Czech Science Foundation project No. 17-27514Y, and by the project EFSA-CDN (No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by ERDF.*

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# SEARCHING FOR ANTICANCER PROPERTIES - PRELIMINARY EVALUATION OF ANTICANCER ACTIVITY OF IMIDAZOTHIAZINONES

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Cancer is still the second most common cause of death in Europe in last few years. Since year 2002 incidence and mortality on account of all types of cancer in the World increased rapidly. [1,2]

The National Cancer Institute (NCI) is the part of the United States National Institute of Health. The Institute was established in 1937 and from that time is addressed for research and training needs for cause, diagnosis, and treatment of cancer. Developmental Therapeutics Program (DTP) is the drug discovery and development arm of the NCI. One of DTP lead programs is anti-cancer compound screening program for identifying novel chemical leads and biological mechanisms of drugs actions. [3]

Imidazothiazinones are interesting scaffolds. They were reported to be antagonists of GPR18 orphan receptor, that made them the potential drug target for inflammatory diseases and cancer immunotheraphy. [4, 5] Therefore we decided to test the series of imidazothiazinones for they anticancer properties.

As the result of our cooperation with NCI, a series of imidazothiazinones, were accepted for a primary pharmacological screening in DTP program. Compounds were tested in one concentration (10 μM) at 60 different human cancer cell lines: prostate, breast, ovarian, colon, renal, central nervous system, non-small cell lung cancer, melanoma and leukaemia. Evaluated structures exhibit low, moderate or high effect on cancer cells growth.

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# SYNTHESIS, BIOLOGY, COMPUTATIONAL STUDIES AND IN VITRO CONTROLLED RELEASE OF NEW ISONIAZID-BASED ADAMANTANE DERIVATIVES

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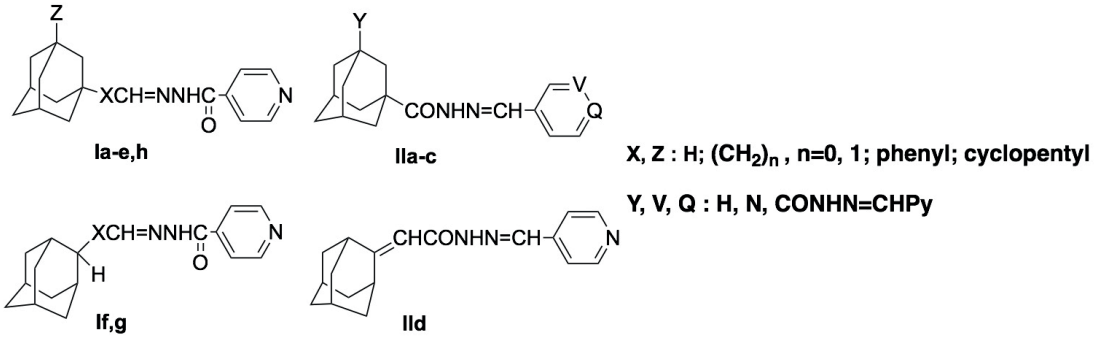
Alongside HIV/AIDS and malaria, tuberculosis (TB) is one of the three major microbial lethal threats to human history in developing and industrialized countries worldwide. Besides the gravity of the disease, TB receives insufficient funding and research on new drugs is less intense compared to other 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 $\mu$g/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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# SYNTHESIS AND EVALUATION OF NEW NIFURTIMOX-ADAMANTANE ADDUCTS WITH TRYPANOCIDAL ACTIVITY

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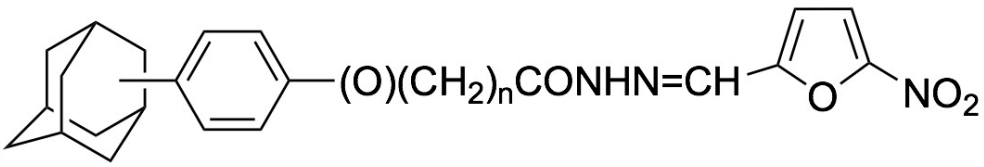
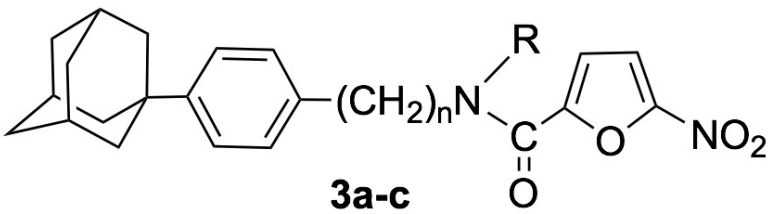
The available drugs against neglected tropical diseases (NTDs) are characterized by toxicity, limited efficacy and increasing resistance. Indicatively, nifurtimox and benznidazole, which are used against the Chagas disease, can cause severe side-effects and treatment is often unsuccessful. This has led the World Health Organization (WHO) to coordinate public sector and private partnerships as part of a global effort to develop new and safer dugs.

Over the past 10 years we have sought to develop adamantane derivatives with antitrypanosomal potency[1-3]. Herein, the synthesis and pharmacological evaluation of the C-1 substituted adamantane hydrazones **1a**-**d**, their C-2 substituted isomers **2a**-**d**and the C-1 substituted adamantane furanoic carboxamides **3a**-**c** is described. Thenifurtimox-adamantane hydrazone adducts present higher trypanocidal activity than the parent drug, nifurtimox. The structural modification comprising of a phenyl ring insertion 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 thebest selectivity is the phenylacetoxy hydrazone **1b**($EC_{50}$=11 ± 0.9 nM and SI=770).




**1a-d, 2a-d** n=0,1,2




**3a-c**

n=1,2
R=H,Bn

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# NOVEL MULTI-TARGET AGENTS TACKLING ALZHEIMER'S DISEASE THROUGH CHOLINESTERASES INHIBITION AND NMDA RECEPTOR ANTAGONISM

**F. Javier Pérez-Areales (1), Andreea L. Turcu (1), Marta Barniol-Xicota (1), Caterina Pont (1), Deborah Pivetta (1), Alba Espargaró (2), Manuela Bartolini (3), Angela De Simone (4), Vincenza Andrisano (4), Belén Pérez (5), Raimon Sabaté (2), Francesc X. Sureda (6), Santiago Vázquez (1), Diego Muñoz-Torrero (1)**

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Since memantine, a NMDA receptor antagonist marketed in 2002, any new drug has been approved for Alzheimer's disease (AD) treatment, likely due to the complexity of its pathogenesis, which involves multiple mechanisms and key proteins that are dysregulated. Then, there is a very urgent unmet medical need to be covered by a therapeutic strategy as much efficient as versatile. In this context, multi-target directed ligands have recently emerged as a very promising approach to develop novel small-molecules potentially useful in AD. The power of multi-target chemical entities resides in their ability to hit distinct pivotal targets within such pathogenic network, thereby eliciting simultaneous and synergistic effects.

Herein we report the synthesis and multi-target biological profiling of a novel class of benzohomoadamantane–chlorotacrine hybrids that have been rationally designed to tackle the cholinergic neurotransmitter system by modulation of both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activities, the glutamatergic system by NMDA receptor antagonism, and β-amyloid peptide and tau protein aggregation. These heterodimers combine a benzoadamantane scaffold, recently optimised by our laboratory and endowed with NMDA receptor antagonistic activity in the same range of memantine, with the potent cholinesterases inhibitor 6-chlorotacrine. Both moieties are connected by oligomethylenic linkers of two different lengths and different attachment positions, pursuing a dual site binding within AChE and the exploration of the binding mode in the NMDA receptor, respectively. The novel compounds turned out to be highly potent inhibitors of *h*AChE (0.34–1.96 nM) and *h*BChE (0.021–2.36 μM), and NMDA receptor antagonists (0.89–8.29 μM), but rather weak $A\beta_{42}$ and tau aggregation inhibitors. Interestingly, the most potent compounds are 44-fold more potent AChE inhibitors than the parent 6-chlorotacrine and 2-fold more potent NMDA receptor antagonists than memantine, and constitute promising leads for AD drug discovery.

# BIOLOGICAL DIFFERENCES AMONG THE CDK4/6 INHIBITORS

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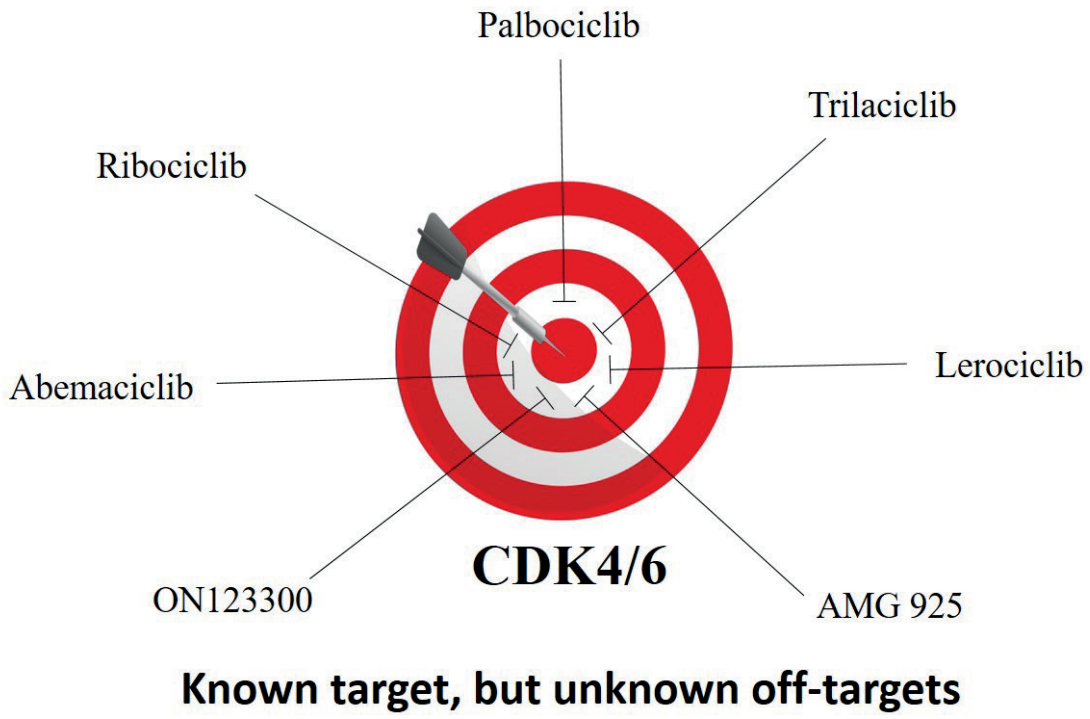
CDK4 and CDK6 are cyclin-dependent kinases that control the transition between the G1 and S phases of the cell cycle, which are typically deregulated and overactive in cancer cells [1]. Three inhibitors of CDK4/6 (Palbociclib, Ribociclib, and Abemaciclib) have been approved for the treatment of breast cancer and several others CDK4/6i (e.g. ON123300, Trilaciclib, Lerociclib, AMG925) entered clinical trials [2, 3].

All drugs mentioned above share similar structural motifs and are reported to have similar mechanisms of action (mostly CDK4/6 inhibition) although recent *in vitro* data pointed at some distinctions. Selectivity studies clearly confirmed differences in potential off-target kinases [4, 5, 6]. Our aim is to study differences in CDK4/6i at cellular level and show important features that could be therapeutically (dis)advantageous for the potential therapy and to improve the knowledge leading to the possibility of choice of ideal CDK4/6i as a drug.

CDK4/6i usually arrest proliferation of cells in G1 phase of the cell cycle without significant induction of the cell death during the short treatment. Our data showed that some CDK4/6 inhibitors cause G2/M block of the cell cycle after 24 h treatment, importantly also in Rb-negative cells.

Further, we observed considerable differences between CDK4/6i in acute myeloid leukemia cell lines, namely EOL-1 and MV4-11 cells bearing oncogenic PDGFR and FLT3-ITD mutation, respectively. We found, that while phosphorylation of STAT proteins in studied cells were significantly reduced after the short treatment with Trilaciclib and ON123300, no effect was observed in the cells treated with Palbociclib, Abemaciclib or Ribociclib.

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# OXAZOLIDINONES AS NOVEL ANTICONVULSANT AGENTS

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**Introduction & Objectives:** Epilepsy, a disorder of the brain causing seizures, affects about 65 million people globally and 30% of the patients suffer from therapy-resistant epilepsy. Oxazolidinone scaffold is part of the framework of some clinically useful antimicrobial, psychoactive, and anticoagulant agents. It also has anti-cancer and anti-thyroid activities. The objective of this study was to evaluate a series of triazolyl-oxazolidinones for anticonvulsant activity.

**Methods:** Eighteen oxazolidinones were synthesized and evaluated for anticonvulsant activity using the NIH protocol on minimal clonic seizure (6Hz, 3sec) test. Test compounds (100 mg/kg) were pre-administered to mice (n=4) by i.p. injection and then challenged with current delivered through corneal electrodes to elicit psychomotor seizures, at varying times. Neurological toxicity was evaluated by the rotarod test. The $ED_{50}$ (n=8) of 6 compounds (PH066, PH139, PH153, PH162, PH166, PH192) was determined. Compound PH192 with highest protective index (PI), was further evaluated *in vivo* using electrically-induced (6Hz and maximal electroshock (MES)) and chemically-induced (pentylenetetrazole (PTZ) 50 and 100mg/kg) rat seizure models.

**Results:** Nine of the tested compounds showed anticonvulsant activity, protecting between 1-3 mice out of 4. Of the 6 compounds further studied for $ED_{50}$ evaluation, PH66 and PH192 were the most active with $ED_{50}$ (± SEM) values of 52.47 ± 0.52 and 34.03 ± 0.62 mg/kg, respectively. All 6 compounds showed good neurotoxicity profiles with $300 < TD_{50} < 750$ mg/kg. The most active compound PH192 ($ED_{50}$ of 34.5mg/kg) proved to be the least neurotoxic ($TD_{50}$ >500 mg/kg) with a neuroprotective index of >14.7. When pretreated with 100 mg/kg of PH192 for 30 mins, about 75% (mice) and 66.6% (rats) were protected from 6 Hz-induced seizures, while 83.3% (rats) were protected from MES stimulation. PTZ at 50 and 100mg/kg injection produced seizures in all rats and 30 mins i.p. pretreatment with 100 mg/kg PH192 protected 80% rats from PTZ-induced seizures comparable to phenytoin (40mg/kg) protection.

**Conclusion:** PH192, though short-acting, protects against both chemically- and electrically-induced seizures without obvious CNS side effects.

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# DEVELOPMENT OF MACHINE-LEARNING-BASED TOOLS FOR GAINING KNOWLEDGE ABOUT POLYPHARMACOLOGICAL PROFILE OF COMPOUNDS

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The modern era of computer-aided drug design has rapidly shifted from developing computational tools for the search of compounds active towards selected target to the search for structures that possess strictly defined activity profile and are simultaneously active towards several receptors with the provision of inactivity towards set of another proteins at the same time (polypharmacology paradigm). [1] Such an approach is not only supposed to increase the probability of triggering desired biological activity by particular compound, but also can help in getting rid of side effects, when the set of the so-called anti-targets is properly defined.

In the study, we examined the applicability of machine-learning-based tools in the polypharmacological tasks within the antipsychotic profile containing target ($D_2$, 5-$HT_{2A}$, 5-$HT_6$), and anti-target (5-$HT_{2C}$) receptors,[2] and using training/testing datasets extracted from the ChEMBL [3] and in-house databases. Two main paths are taken into account – decomposition of the polypharmacology problem into the respective series of binary tasks and multi-label approach, when particular compound is evaluated in terms of activity towards all targets considered simultaneously. Two types of compounds representations were used in the study – hashed fingerprint (Extended connectivity fingerprint) and key-based ones (MACCS and Klekota&Roth). AdaBoost and Support Vector Machines algorithms were used and effectiveness of the particular approach was evaluated by the Matthews Correlation Coefficient and Balanced Accuracy parameters. Due to the fact that there is a lot of missing data, the separate evaluations target-by-target seem to be more effective approach.

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# A UNIQUE MULTIPLEX HTS ASSAY ENABLES THE DISCOVERY OF A NOVEL PRO-DIFFERENTIATE ANTI COLORECTAL CANCER COMPOUNDS

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Differentiation therapy has been recently revisited as an approach in cancer therapy. Its goals are targeting the aberrant growth, differentiation and cell death programs of cancer cells. Differentiation therapy directs cancer cell toward normal status, inhibiting their proliferation and restoring the apoptotic program without the negative effects of chemotherapy and/or anti angiogenetic therapy.

A ubiquitous marker of cell differentiation in colon epithelial cells is the level of expression and activity of the enzyme called intestinal alkaline phosphatase (ALP). While differentiated intestine epithelial cells express relatively high level of the enzyme, ALP expression in poor differentiated cells is known to be very low, almost negligible.

We used this principle to screen compounds for their ability to induce ALP expression in cancerous cells. To this end we developed a multiplex assay for HTS, where expression of ALP can be measured and normalized to the live cell number in the same sample (CDP/CTG assay). We verified that colon cancer cell lines (HT-29, HCT-116) have very low, if any, expression of ALP. This is in contrast to relatively normal colon cell line CCD-841. HT-29 cell line was selected for the screen since it was repeatedly reported as responding to pro differentiate therapy with Sodium Butyrate.

5790 compounds (from different chemical libraries) were screened for their ability to manipulate ALP expression in HT-29 cells. Potential hits were tested on CCD-841 cells to ensure selective differentiate effect on cancer cells. Compounds were further validated in a dose dependent manner for their effect on pro-differentiating markers expression (E-cad and ZO1). A methyl transferase inhibitor was identified as a compound that enhances differentiation and significantly delay proliferation of HT-29 cells without any effect on normal cells. This is in contrast to known pro-differentiating agents such as entinostat and sodium butyrate that show toxicity in both normal and cancer cells.

Here we show that the CDP/CTG multiplex assay developed in our lab is applicable for HTS screening and allowed us to identify a new target for efficient pro-differentiate therapy of colorectal cancer.

# SYNTHESIS AND BIOLOGICAL PROFILING OF MULTISITE BACE-1/AChE INHIBITORS AS POTENTIAL ANTI-ALZHEIMER AGENTS

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**Alzheimer disease** (AD) is one of the most relevant health problems worldwide, due to the lack of effectiveness of marketed drugs. New therapies with the ability to modify the progression of the disease are urgently needed. The fact that AD is a complex network of interconnected pathological events has led to the notion that concurrent modulation of several key targets of the network will inflict a much more profound effect than modulating one specific single target (1).

We recently developed a lead rhein-huprine hybrid (2,3) with a promising multitarget biological profile, which included an outstanding nanomolar inhibitory activity against BACE-1. According to molecular modelling studies (2,4), a dual site binding at the catalytic site of BACE-1 (huprine moiety) and at a novel transient secondary pocket (rhein moiety) accounted for the high BACE-1 inhibitory potency. A virtual screening campaign from the ZINC database has led to the identification of a number of scaffolds with predicted binding affinity to the secondary floppy pocket of BACE-1. Here we describe the synthesis and biological profiling of a novel class of hybrids, designed by combination of these scaffolds and a huprine moiety to display dual site binding within both BACE-1 and AChE. Apart from the activity of the novel compounds on their primary targets, other activities of interest for anti-Alzheimer agents have been evaluated, namely butyrylcholinesterase inhibition, tau and Aβ42 aggregation inhibition, and metal chelating properties, as well as their brain permeability (PAMPA-BBB assay) and toxicity (zebra fish model).

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# DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW RNA LIGANDS AS INHIBITORS OF ONCOGENIC MICRORNAS PRODUCTION

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MicroRNAs (miRNAs) are a class of small non-coding RNAs that act as regulators of gene expression at the post-transcriptional level. Increasing evidence has indicated that the deregulation of miRNAs expression is linked to various human cancers and therefore, miRNAs represent a new class of potential drug targets. In this context, we focused on the discovery of new inhibitors of oncogenic miRNAs production. We choose to target two miRNAs (miRNA-372 and miRNA373) implicated in various types of cancer, such as gastric cancer. Their precursor pre-miRNAs are overexpressed in cancer cells and lead to mature miRNAs after cleavage of their stem-loop structure by the enzyme Dicer in the cytoplasm.[a]

Our group previously demonstrated that conjugates of the aminoglycoside neomycin with artificial nucleobases were able to efficiently inhibit the production of oncogenic miRNAs upon binding to their precursors and inhibiting Dicer-mediated processing. This activity has been directly linked to a decrease in the production of oncogenic miRNA-372 and -373 in adenocarcinoma cells and the decrease of cancer cells proliferation was observed.[b] While these compounds were efficient inhibitors, their physicochemical properties were not favorable for future therapeutic applications.

Here we describe a new series of drug-like conjugates where the previously employed neomycin was replaced with 2-desoxystreptamine (Figure 1). This latter belongs to neomycin, it is known to be particularly important in the interaction with RNA and bears a reduced size. The synthesized compounds have been studied for their ability to inhibit Dicer processing of pre-miRNAs *in vitro* and for their affinity and selectivity for these targets. We were able to demonstrate that some of these compounds maintain the biological activity of their neomycin analogs opening new perspectives for the synthesis of new efficient and selective RNA binders.

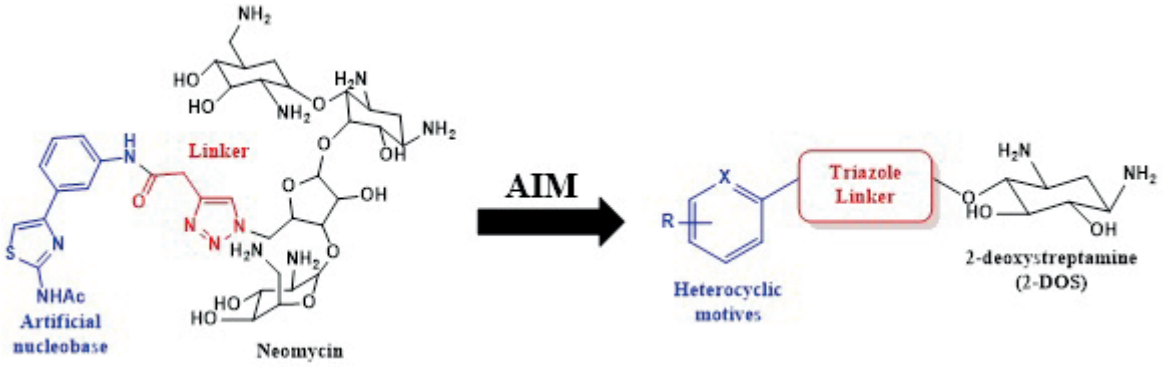


*Figure 1 : New inhibitor structure of oncogenic miRNAs*

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# STEREOCONTROLLED SYNTHESIS AND INVESTIGATION OF THE BIOSYNTHETIC TRANSFORMATIONS OF 16(S),17(S)-EPOXY-PDn-3 DPA

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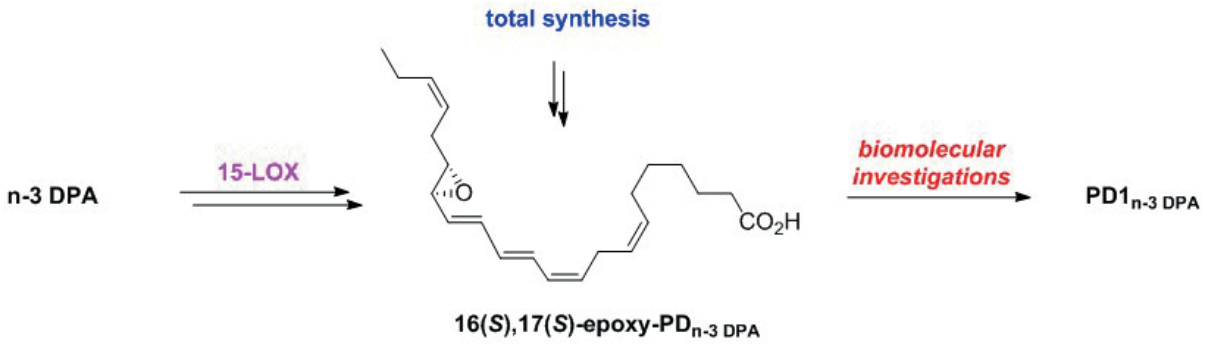
Specialized pro-resolving lipid mediators (SPMs) are biosynthesized during the resolution phase of acute inflammation from n-3 polyunsaturated fatty acids and act as agonists towards G protein-coupled receptors (GPRs).[1,2] Such naturally occurring compounds are of current interest in biomolecular chemistry and drug discovery.[3] $PD1_{n\text{-}3\ DPA}$ was one of the first n-3 DPA-derived SPMs to be reported and itdisplays potent anti-inflammatory and pro-resolving bioactions.[1,4] 16(*S*),17(*S*)-epoxy-$PD_{n\text{-}3\ DPA}$ was prepared by stereoselective total synthesis to investigate the involvement of an epoxide intermediate in the biosynthesis of $PD1_{n\text{-}3\ DPA}$ from n-3 docosapentaenoic acid. Based on results from LC/MS-MS metabololipidomics we demonstrated that 16(*S*),17(*S*)-epoxy-$PD_{n\text{-}3\ DPA}$ is converted by human neutrophils to $PD1_{n\text{-}3\ DPA}$, confirming the role of this epoxide in the biosynthesis of $PD1_{n\text{-}3\ DPA}$.[5] Additionally, we found that 16(*S*),17(*S*)-epoxy-$PD_{n\text{-}3\ DPA}$ regulates the formation of the potent neutrophil chemoattractant $LTB_4$, with equal potencies to that obtained with $PD1_{n\text{-}3\ DPA}$.[5]

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# DIVERSITY-ORIENTATED SYNTHESIS OF MACROCYCLIC HETEROCYCLES USING DOUBLE SNAr (SNACK MACROCYCLISATION).

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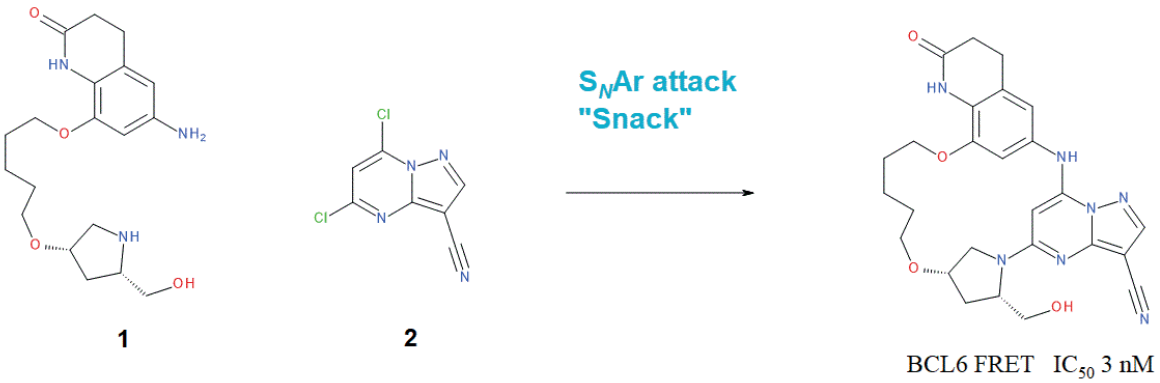
Macrocyclic rings provide a compromise between structural pre-organization and flexibility that can facilitate modulation of novel, “difficult” targets that contain large, shallow and featureless binding sites such as protein-protein interactions (PPIs). However, macrocycles can also have low synthetic tractability, for example the macrocyclisation step is often low yielding and requires high dilution conditions to diminish formation of undesired side products that derive from intermolecular reactions.

This presentation will discuss how we successfully used macrocycles to inhibit the PPI between BCL6 and its corepressors. In terms of synthesis we have developed a novel, efficient and high yielding strategy for the construction of diverse macrocyclic scaffolds (Scheme 1). Our approach was based on the double aromatic nucleophilic substitution reaction between pre-assembled, masked di-nucleophiles (**1**) with corresponding heterocyclic di-electrophiles (**2**). Using this double $S_NAr$ attack (Snack) strategy the macrocyclic linker and the heterocycle could be readily varied and, as a result, diverse highly potent ($IC_{50}$ the PPI between BCL6 and its corepressors in in vitro cell lines.

**Scheme 1**




**1** **2**

# ADME-TOX PROFILING OF A NEW BIPHENYLMATHANE SCAFFOLD BASED ON A MULTI-TARGET APPROACH TO TREAT ALZHEIMER'S DISEASE

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The Alzheimer's Disease (AD) etiopathology involves alterations of several physiological pathways, both in peripheral and central nervous system regions, such as decreased lipid metabolism, lowered tau phosphorylation, increased neuro-inflammation, and unbalanced autophagy. This multiple impairment leads to an aberrant protein aggregation and uncontrolled neuronal cell death, resulting in the well-known decline of cognitive functions. To date, different mono-targeting approaches have been investigated to treat AD, but none of them seems to achieve the desired effect of reversing it. There is growing evidence implicating the role of autophagic flux as a crosslinking effector in neurodegenerative disorders. Moreover, a marked impairment of this process has been observed in several AD models, suggesting that it could play a pivotal role its development and progression [1].

We have designed and characterized a new class of synthetic small molecules with a biphenylmethane scaffold, namely SG compounds to target this. Among them, SG-2 was identified as a promising hit-compound able to promote a neuroprotective effect in a nematode model of AD (unpublished results). Moreover, SG-2 showed an improvement in learning and memory when systemically administered to CD-1 mice at sub-micromolar doses, and to promote *in vitro* autophagy, a key player for neuronal plasticity [2-3].

Recently, several SG-2 analogues have been designed and synthetized with the aim to increase the chemical diversity of SG-2. In order to evaluate the phenotypic profile of these compounds, we performed *in vitro* screening on these analogues. This included a comprehensive panel of ADME-Tox assays in order to identify the most promising compound for progression in the drug discovery value chain. These assays included autophagy, cytotoxicity in four different cell lines (MCF-7, HEK293, hTERT, and U2-OS), *h*ERG liability, CYP450 inhibition (2C9, 2C19, 2D6, and 3A4) and off-target liability against HDAC6, HDAC8, SIRT7, PDE4C1, Aurora B kinase, PKC, and PANK. More than 30 compounds were tested; notably, ten of the tested SG analogues showed a clean and safe toxicological, pharmacological and pharmacokinetic profile. Further *in vitro* and *in vivo* studies will be planned to investigate the safety of these novel biphenylmethane scaffold-based molecules in neurodegenerative disorders such as AD.

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# EMERGING THERAPIES FOR ACUTE MYELOID LEUKAEMIA USING HDHODH INHIBITORS

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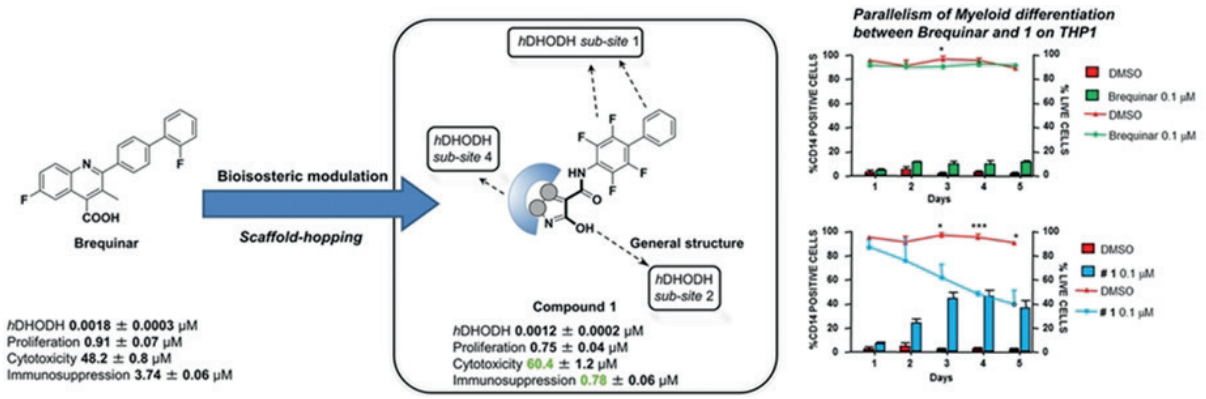
Bio(iso)steric replacement is a widely used approach in medicinal chemistry to improve the bioavailability, selectivity, potency and other properties of a lead compound. Since 2006, the authors have investigated hydroxylated heterocyclic systems, in order to create a sophisticate tool able to bioisosterically mimic the carboxylic and other acidic functions. The application of this bioisosteric tool, that cover a wide range of pKa and chemiodiversity, led to new anticancer, antiparasitic, immunosuppressive and differentiating agents.1 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 Following that early affords, in this occasion we are presenting a new generation of inhibitors (Figure 1) able to reach the brequinar hDHODH potency levels. 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. 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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# DRUGGING THE FBW7 E3 LIGASE WITH A FRAGMENT-BASED APPROACH

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Fbw7 is an important E3 ligase and one of the most commonly deregulated proteins in human cancers. Six per cent of cancers have mutations in the *fbw7* gene. In one hand, the loss of activity of the mutated Fbw7 results in a loss of its tumor suppressor function and an upregulation of the natural and oncogenic substrate proteins, such as c-Myc, cyclin-E, and Notch.[1] On the other hand, the inhibition of Fbw7 has been proposed as an approach to sensitize cancer stem cells to chemotherapies.[2] Given the key role of Fbw7 in tumorgenesis, a small molecule directly targeting Fbw7 would have a large impact on the clinic. However, so far, no potent small-molecules that directly bind to Fbw7have been reported, in part because modulating their activity and regulation requires targeting protein-protein interactions.[3]

Our goal is to identify and characterize fragments that bind to the Fbw7 E3 ligase and can be further developed as chemical probes. These fragments may turn *on* or *off* the activity of the protein. Fbw7 binders could serve as anchors to develop disease-specific PROTAC molecules, leading to proximity-induced ubiquitylation and subsequent degradation of proteins of interest.[4] Our group has built a library of around 700 fragments. Surface Plasmon Resonance (SPR) has been carry out. Potential fragment-hits have been identified and they are being validated using orthogonal biophysical techniques. Furthermore, in order to elucidate the binding mode of the fragments, it is crucial to perform x-ray crystallography. Crystal structure of fragments binding to the protein will not only show the key points for the interaction but also it can provide the starting point for a rational design to grow the molecules in order to improve their affinity and specificity.

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# DESIGN AND SYNTHESIS OF FLUORESCENT PROBES FOR MONITORING ECTO-5'-NUCLEOTIDASE (CD73) – A BIOMARKER FOR CANCER CELLS

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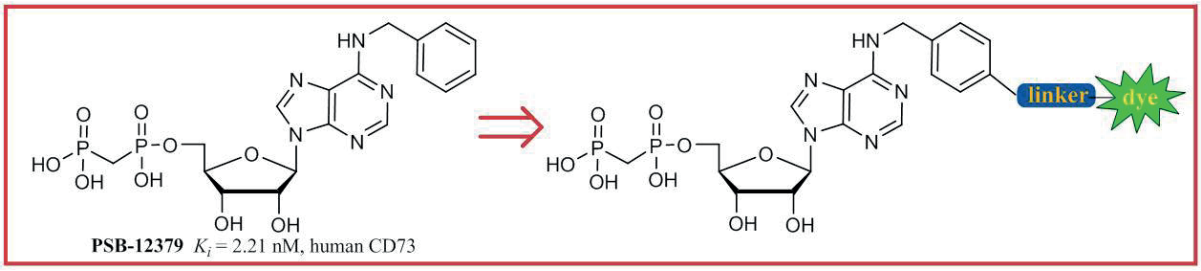
*Ecto*-5'-nucleotidase (CD73) is a member of the *ecto*-nucleotidase family, which catalyzes the hydrolysis of nucleoside monophosphates, mainly AMP, producing the signaling molecule adenosine. Further *ecto* -nucleotidases include the nucleoside triphosphate diphosphohydrolases (NTPDases; subtypes 1, 2, 3 and 8), the nucleotide pyrophosphatases/phosphodiesterases (NPP1-4) and the alkaline phosphatases (APs).[1] CD73 is often co-localized with adenosine receptors. CD73 inhibitors reduce extracellular adenosine levels, which results in an indirect blockade of adenosine receptor activation. Many tumor cells over-express *ecto*-nucleotidases, which metabolize pro-inflammatory ATP into anti-inflammatory, immunosuppressive, tumor growth-stimulating, angiogenic adenosine.[2]Therefore, *ecto*-nucleotidases possess potential as novel drugs, e.g. for cancer (immuno)therapy and for the treatment of neurodegenerative diseases.

To monitor the expression levels of CD73, a fluorescent marker molecule with a high binding affinity that can be used instead of an antibody, is highly desirable. The ADP analogue $\alpha,\beta$-methylene-ADP (AOPCP, $K_i$ = 88.4 nM, human CD73) was the first described potent competitive inhibitor of CD73.[3,4] Since its discovery, significantly more potent AOPCP-based inhibitors have been developed by our group that display high selectivity and metabolic stability.[4] One of these compounds, PSB-12379, was selected as a lead structure to develop potent fluorescent CD73 antagonists with high binding affinity. The idea was to attach a fluorescent dye to the benzyl ring in the $N^6$-position of the adenine core structure via a linker moiety. To optimize the binding properties of the target compounds, multiple factors have to be taken into account, including the linker length, the lipophilicity of the linker, the connection between the linker and the CD73 inhibitor, and the fluorophore. The obtained fluorescent CD73 inhibitors will be useful tools for research and diagnostic applications.




**PSB-12379** $K_i$ = 2.21 nM, human CD73

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# THE PROTEIN CORONA FORMATION- A CRUCIAL FACTOR IN UNDERSTANDING INHIBITORY ACTIVITY OF [60]FULLERENE DERIVATIVES

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Recently we have demonstrated that fluorescently-labelled [60]fullerene derivatives are able to extravasate more into orthotopic breast tumor tissues, than into contralateral mammary fat pad [1]. Here, we propose that glycosylation of [60]fullerene core will promote cancer targeting of engineered carbon nanomaterials, due to overexpression of glucose transporter membrane proteins (GLUTs) in several cancers, including pancreatic [2]. The water-soluble glycofullerenes **GF1** and **GF2** were synthesized using two-step modified Bingel-Hirsch methodology. Interestingly, we have identified buckyballs as a novel class of non-receptor Src kinases inhibitors. The evaluated compounds were found to inhibit Fyn A and BTK proteins with $IC_{50}$ values in the low micromolar range, with the most active compound at 39 μM. Moreover we have demonstrated that formation of protein corona on the surface of [60]fullerene derivatives is changing the landscape of their activity, tuning the selectivity of obtained carbon nanomaterials towards Fyn A and BTK kinases. The performed molecular biology studies revealed no cytotoxicity and no influence of engineered carbon nanomaterials to the cell cycle of PANC-1 and AsPC-1 cancer cell lines. Incubation with the tested compounds resulted in the cellular redox imbalance triggering the repair systems and influenced on the changing of the protein levels.

**Maciej Serda and Katarzyna Malarz thank National Science Center (Poland) for the support (SONATA UMO-2016/23/D/NZ7/00912 and PRELUDIUM 2016/23/N/NZ7/00351 grants).**

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# SNAPSHOTS OF THE FORMATION OF A QUINONE METHIDE REACTIVE SPECIES AT A SECONDARY SITE OF THIOREDOXIN GLUTATHIONE REDUCTASE FROM SCHISTOSOMA MANSONI

**Ilaria Silvestri (1), Haining Lyu (2), Francesca Fata (1), Maria Benedetta Mattei (1), Paul Banta (2), Anna Scortica (1), Luana Di Leandro (1), Matteo Ardini (1), Rodolfo Ippoliti (1), Andrea Bellelli (3), Gregory R. J. Thatcher (4), Valentina Z. Petukhova (4), Pavel A. Petukhov (4), David L. Williams (2), Francesco Angelucci (1)**

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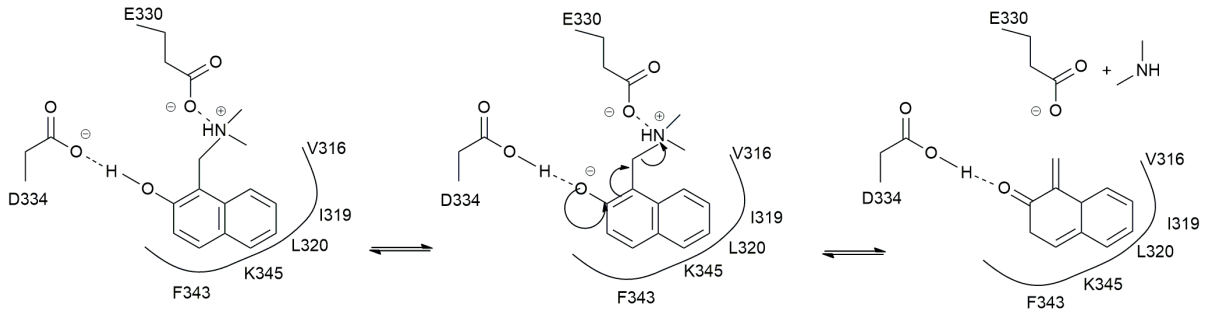
Covalent modification represents a successful approach for inactivation of therapeutically relevant enzymes. Suicide substrates, stable molecules that require bioactivation by the specific enzyme target, represent a seductively attractive approach to enzyme inhibition, since they are generally devoid of off-target toxicity *in vivo* . Whereas most suicide substrates are converted to a reactive electrophile at the enzyme active site, adventitious binding sites may also theoretically lead to bioactivation *in situ*. Thioredoxin glutathione reductase (TGR), a selenocysteine-containing enzyme, is one of the promising drug targets to treat schistosomiasis, a human parasitic disease caused by *Schistosoma mansoni* (SmTGR) and other members of *Schistosoma* family of worms. Utilizing hits selected from a high throughput screening campaign, time-resolved X-ray crystallography, and protein mutagenesis coupled with functional studies, we find that 2-naphthol-based derivatives are bound to a novel site of SmTGR and transformed to covalent modifiers. Interestingly, this site does not appear to play a direct role in the enzymatic machinery of SmTGR. The site-specific amino acid environment facilitates the adventitious transformation of the initial molecule into an *o*-quinone methide (oQM) as shown below. The resulting QM is likely to react with the nucleophilic functional residues of SmTGR, inhibiting its enzymatic activity. This study suggests a general approach to design of novel suicide substrate inhibitors of SmTGR as well as human orthologues identified as chemotherapeutic targets for cancer and inflammatory disorders.

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# DEEP LEARNING APPLIED TO LIGAND-BASED DE NOVO DESIGN: A REAL-LIFE LEAD OPTIMIZATION CASE STUDY

**Quentin Perron (1), Olivier Mirguet (2), Anne Rojas (2), Arnaud Gohier (2), Pierre Ducrot (2), Philippe Gloanec (2), Marie-Pierre Bourguignon (2), Patricia Sansilvestri (2), Hamza Tajmouati (1), Nicolas Do Huu (1), Yann Gaston-Mathé (1), Françoise Gellibert (2)**

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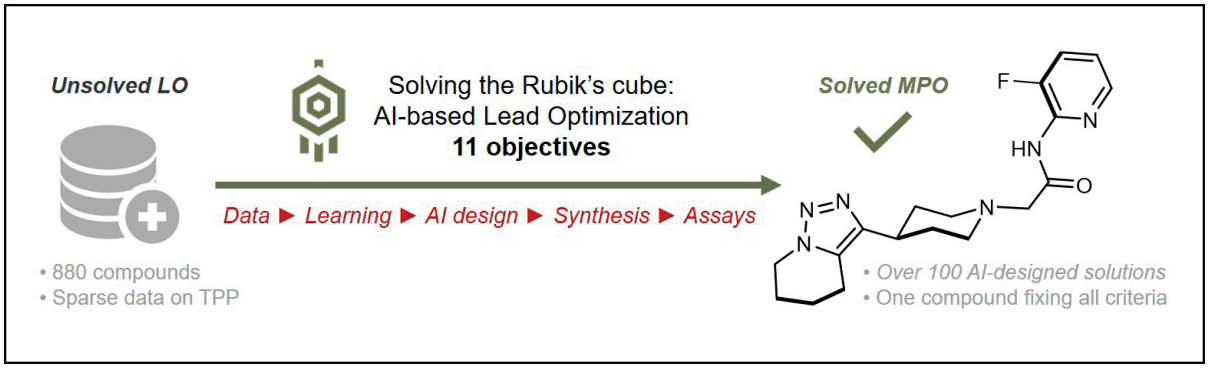


Despite existing ligand- and structure-based *de novo* design methods, Multi-Parameter Optimization (MPO) remains a major challenge in New Chemical Entity (NCE) drug discovery projects, and the inability to identify molecules meeting all the criteria of lead optimization (LO) is an important cause of NCE project failure.[1-2] Lately, promising results have been reported for deep learning generative models applied to *de novo* molecular design.[3] Yet, to our knowledge, no report to date has been made of the value of this new technology for addressing MPO in a complex, real life drug discovery project.

Starting from a data set of 880 molecules tested on 11 bioassays, single task QSAR models were developed. Then, our deep generative algorithm has been used to design virtual molecules fulfilling all 11 objectives according to a multi-objective fitness function built from the predictive QSAR models. From 150 AI-designed compounds, 11 have been synthesized & assessed *in vitro*. Amongst them, one met simultaneously all objectives of the project, and 2 met 10/11 objectives just below the required threshold, within the margin of error of the assay, regarding the last objective. To our knowledge, this is the first successful application of deep learning to *de novo* design, to solve an MPO issue in an actual drug discovery project, moreover on a large number of objectives.

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# A CHEMICAL TOOLBOX FOR CEREBLON-DIRECTED PROTACS

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The proteolysis targeting chimera (PROTAC) concept is currently receiving major attention in drug discovery field as it holds tremendous potential in the therapy of different human diseases.[1,2] In addition, it also represents a powerful tool for protein function studies in vivo.[3] PROTAC strategy uses a heterobifunctional molecule comprised of a small-molecule ligand (binding to a protein of interest) and another small molecule ligand (binding to an endogenous E3 ligase). If designed successfully, PROTAC molecules hijack the endogenous ligase and the ubiquitin proteasome system to degrade protein(s) of interest.[4]

Despite that more than 600 E3 ligases exist, only a few are utilized in PROTACs. Particularly, cereblon (CRBN) is receiving a lot of attention, because its ligands, i.e. thalidomide, lenalidomide, and pomalidomide, are present in numerous PROTACs. Because the number of publications in this field is increasing exponentially, we decided to summarize major chemical approaches to prepare CRBN-targeting conjugates. We designed a series of toolbox compounds with a common feature, which is the connection of the linker at the 4-amino group of pomalidomide. Various polyalkylene ether linkers and several terminal functional groups for conjugation were used in the design of this 'MedChem' PROTAC toolbox.[5] In addition, we highlighted different opportunities for the expansion of this toolbox towards heterobifunctional molecules, e.g. with biotin, fluorescent, hydrophobic and peptide tags.

The presented set of compounds is useful owing to its broad applicability for PROTAC design and we hope that it will enable rapid generation of PROTAC precursors and thus further advancements of this quickly evolving field.

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# MEDICINAL CHEMISTRY TOOL BOX FOR RAPID ASSEMBLY OF PROTAC MOLECULES

**Jasper Springer, Marcel Scheepstra, Patrick Oude Alink, Yannick Smits, Toine van den Bergh, Rob Winkel, Koen Hekking, Luc van Hijfte, Rutger Folmer**

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Proteolysis targeting chimeras (PROTACs) have recently received significant attention as a new modality for therapeutic intervention (recently reviewed in [1,2]). The technology is based on hijacking E3 ligases to tag a protein of interest with ubiquitin for degradation by the proteasome. This involves the synthesis of a chimeric ligand in which a compound that binds to the protein target of interest is linked to a second molecule that binds an E3 ligase (usually either cereblon or VHL).

The linking of the two small molecule ligands is typically done through a polyethylene glycol (PEG) based linker, consisting of 3 to 6 glycol units. The optimal linker length as well as the level of lipophilicity need to be empirically determined using a relevant cellular assay (based on detection of protein amount, or a more functional assay).

PROTAC molecules are typically around 1 kDa in size, and not seldom link together two molecules with mediocre physico chemical properties (notably high LogP, low solubility). As a result, the synthesis, analysis and purification of these compounds can be more challenging than is the case for traditional small molecule ligands.

To address this challenge, we have developed a modular chemistry toolbox in which different linking strategies can be coupled with optimised analytical routines. This approach allows for the rapid assembly of a comprehensive set of different PROTAC molecules for any new target for which a ligand exists.

In our view, this approach can significantly speed up the development of potential PROTAC drugs, a process that can be very laborious with the currently described tools.

In addition, we are developing novel linkers that go beyond PEG, with the goal of fine-tuning the properties of the resulting bivalent compound.

An overview of our activities in this area will be presented.

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# ON RESIN CLICK CHEMISTRY Cu (I) MEDIATED SYNTHESIS OF NOVEL OPIOID AGONISTS

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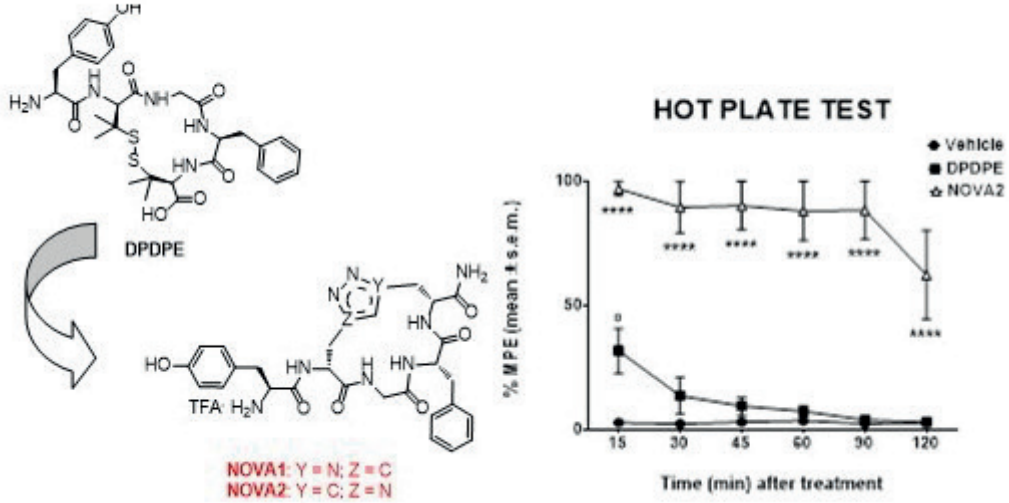
DPDPE, a selective delta-opioid agonist represents a mile stone in the opioid peptide research and it is widely used as standard for biological tests [1,2]. Here, we report the total synthesis of two DPDPE analogues, which entails the solid-phase synthesis of two enkephalins precursor chains, followed by the $Cu^{I}$-catalyzed azide-alkyne cycloaddition. Products were obtained in good yields after simple cleavage and RP-HPLC purification. An efficient synthetic methodology has been probed to readily afford these cyclic peptides via SPPS on resin *side chain to side chain cyclization* involving a CuAAC reaction leading to the formation of a triazole bridge, a useful tool to constrain peptides. Both compounds were tested for specific displacement of triziated opioid standards. **NOVA2** showed a good affinity for mu-opioid receptor and is able to stimulate the G protein with high efficacy and potency ($EC_{50}$ 12.9 nM, Emax% 87.3%). **NOVA2** was also tested *in vivo* recording an exceptionally good activity and long lasting analgesic effect when compare to DPDPE. Owing to its redox stability and dissimilarity to common natural building blocks, improved pharmacokinetic properties can be expected for this disulphide surrogate, which may explain the long-lasting antinociceptive activity, well beyond that of DPDPE.

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# SYNTHESIS AND STRUCTURAL STUDIES OF D2AAK1_1 AS DOPAMINE D2 RECEPTOR ANTAGONIST

**Piotr Stępnicki (1), Agata Bartyzel (2), Magda Kondej (1), Tomasz M. Wróbel (1), Andrea G. Silva (3), Dariusz Matosiuk (1), Marián Castro (3), Agnieszka A. Kaczor (1,4)**

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In search for novel potential antipsychotics, structure-based virtual screening aimed at identifying dopamine $D_2$ receptor antagonists was performed. Among others, compound D2AAK1 was found and then subjected to detailed *in vitro*, *in silico* and *in vivo* investigation. It is a promising multi-target lead structure with nanomolar affinity to a number of dopamine and serotonin receptors with antipsychotic, anxiolytic and procognitive activity *in vivo* [1,2]. Compound D2AAK1_1 was designed as a modification of the lead structure D2AAK1 and synthesized in the reaction of indole and 1-[(furan-2-yl)methyl]piperidin-4-one in methanol/KOH. This compound has affinity to human dopamine $D_2$ receptor with $K_i$ of 257 nM.

The aim of studies was structural characterization of the compound D2AAK1_1. In particular, X-ray studies, molecular docking and molecular dynamics were performed.

The studied compound crystallizes in the centrosymmetric monoclinic space group $P2_1/c$. The molecule adopts a non-planar conformation as indicated by a dihedral angle of 86.1° formed between planes of furan-2-ylmethyl group and indole moiety. The structure of compound is stabilized by a N1-H1N···N2 hydrogen (dD···A = 2.989(3) Å) bonds which leads to formation of one-dimensional ribbons running parallel to the [010] direction (C(8) graph-set motif).

The studied compound was docked to the novel X-ray structure of the human dopamine $D_2$ receptor in the inactive state (PDB ID: 6CM4) and established the main contact between its protonatable nitrogen atom and Asp(3.32) of the receptor as expected for orthosteric ligand of aminergic GPCRs. The obtained binding pose was stable in molecular dynamics simulations.

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# STRUCTURAL MODIFICATIONS OF 1-(ARYLIMIDAZOLIN-2-YL)-3-ARYLUREAS

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An extremely important challenge for today's medical chemistry is to find such compounds that would guarantee an equally strong analgesic effect as opiates, but at the same time would be deprived of their typical side effects. This would certainly enable widespread and safe use of such painkillers, while improving the comfort of life of patients suffering from chronic pain.

Series of 1-(arylimidazolin-2yl)-3-arylureas synthesized by Matosiuk and co-authors showed analgesic properties [1]. Their high affinity towards μ opioid receptor was evaluated on binding assay tests. Behavioral tests on animals confirmed their great antinociceptive activity and low toxicity. Moreover, the compounds did not show side effects typical for opiates. Pharmacological examination suggested that this new compounds may have other mechanism of activation of μ receptors than morphine-like analgesics.
The main aim of our work was to introduce structural modifications of the compounds that would improve their pharmacokinetic properties and fitting to the active center of opioid receptor. By using homologation and chain branching we have obtained a number of new 1-aryl-2-iminoimidazoline-2 derivatives with urea moiety.
The synthesis of the title compounds was achieved by a reaction of arylamines, triphosgene and appropriate 1-aryl-2-iminoimidazolines-2 in dry toluene (Fig. 1). Structures of the final products were identified by their 1H-NMR spectra and elemental analysis.

All synthesized compound are under biological evaluation for their affinity and mechanism of action towards opioid receptors.

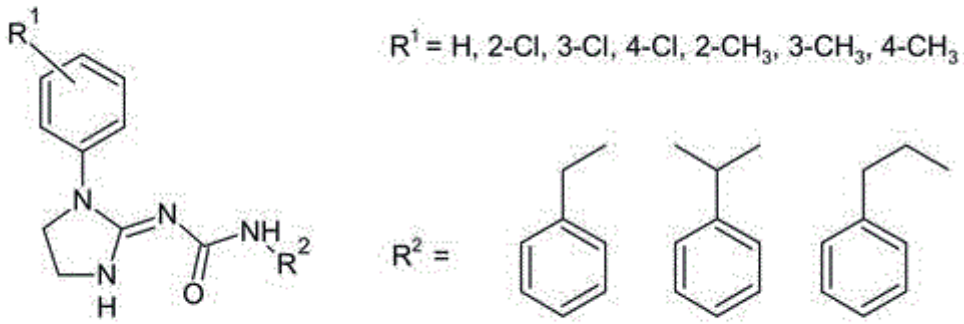


Fig. 1

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# BETA-SECRETASE AND BUTYRYLCHOLINESTERASE INHIBITORS AS POTENTIAL MULTI-TARGETED LIGANDS AGAINST ALZHEIMER'S DISEASE

**Dawid Panek (1), Anna Pasieka (1), Natalia Szalaj (1), Justyna Godyn (1), Jakub Jonczyk (1), Damijan Knez (2), Anna Wieckowska (1), Marek Bajda (1), Stanislav Gobec (2), Barbara Malawska (1)**

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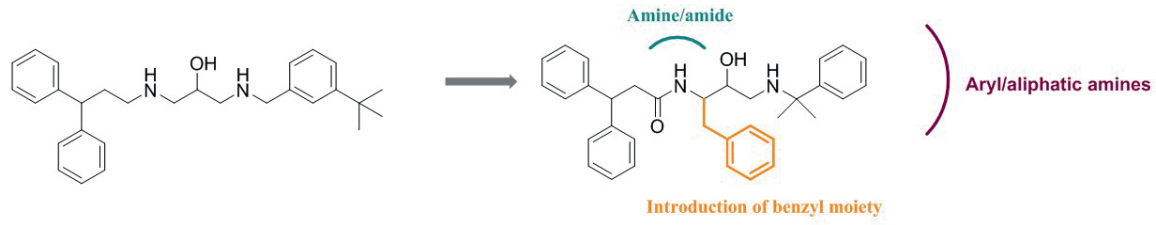
Alzheimer's disease (AD), the most frequent cause of dementia, is a fatal and incurable neurodegenerative disorder, which still remains an unmet medical need. The etiology of AD is not completely understood, probably because the disease is heterogeneous, and is caused by complicated combination of ageing, genetic and environmental risk factors. This complex pathogenesis of AD has prompted the researches to develop compounds, which affect several AD-relevant biological targets simultaneously. In recent years, this multi-target ligands strategy has made great progress in the field of anti-AD drug research and development.[1]

In our research we aimed to develop new effective multifunctional compounds as potential anti-AD agents. Previously, we successfully identified lead structure DAW205 that acts as a multifunctional ligand with the inhibitory activity against beta-secretase (BACE-1), butyrylcholinesterase (BuChE), tau and β-amyloid aggregation (Figure 1).[2] Based on this structure and structures of well-known BACE-1 inhibitors (GRL-8234, KMI-1303), we designed a new series of hydroxyalkalylamine derivatives with the benzyl moiety to improve BACE-1 inhibitory potency. The series of amine and amide derivatives containing 1-amino-4-phenylbutan-2-ol pharmacophore were synthesized and tested *in vitro*. Among the new compounds, we successfully identified more potent dual BACE-1 and BuChE inhibitors with β-amyloid anti-aggregating properties.




**DAW205**
*h*BACE-1 $IC_{50}$ = 41.6 µM
*Eq*BuChE $IC_{50}$ = 2.92 µM
$A\beta_{1-42}$ aggr. inh. = 88.2 % (10 µM)
Tau aggr. inh. = 53.8% (10 µM)

**DAW395**
*h*BACE-1 $IC_{50}$ = 8.86 µM
*Eq*BuChE $IC_{50}$ =3.23 µM
$A\beta_{1-42}$ aggr. inh. = 58.2 % (10 µM)

**Fig. 1. Design strategy of 1-amino-4-phenylbutan-2-ol derivatives.**

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# NOVEL ACTIVE PIPERAZINE DERIVATIVES AS HISTAMINE H3 RECEPTOR LIGANDS

**Katarzyna Szczepańska (1), Tadeusz Karcz (1), Szczepan Mogilski (2), Kamil J. Kuder (1), Stefanie Hagenow (3), Magdalena Kotańska (2), Holger Stark (3), Katarzyna Kieć-Kononowicz (1)**

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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 $\alpha_1$ receptors was also carried out.

We kindly acknowledge the generous support of National Science Center, Poland granted on the basis of decision No. 2016/23/N/NZ7/00469.

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# NEW PERSPECTIVE ON QUINOXALIN-2,3-DIONES AS SELECTIVE ANTAGONISTS OF AMPA/KAINATE RECEPTORS

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Fast excitatory synaptic transmission in the CNS relies almost entirely on the neurotransmitter glutamate and its family of ion ligand-gated channel receptors (*i*GluRs). The family of *i*GluRs is divided into three functionally distinct subclasses: NMDA, AMPA and kainate receptors. Structurally, AMPA-receptors are cation-selective tetrameric heterooligomers formed by combinations of the highly homologous subunits GluA1-4, while kainate receptors are tetrameric assemblies of GluK1-5 subunits.

A group of quinoxalin-2,3-diones is known for their inhibition of ionotropic glutamate receptors action. Within the past twenty years several compounds with this structure have entered clinical trials, showing neuroprotective effects in experimental stroke and in epilepsy models. On the other hand, it has been proved for other chemical groups that competitive AMPA/kainate antagonists may have a clinical potential for the management of chronic pain, including migraine and neuropathic pain.

Many glutamate ligands derived from quinoxalin-2,3-dione scaffold have been shown to bind to NMDA, AMPA and/or kainate receptors, however, only a few of them displayed a selective profile of affinity. The present project is a continuation of earlier studies on potent and selective competitive AMPA and/or KA receptors ligands. In order to map out molecular determinants for the competitive blockade of selected kainate receptor subtypes, a series of quinoxalin-2,3-dione derivatives was designed and docked to available X-ray structures of AMPA and kainate receptors ligand binding domain. The best-scored docking poses were carefully inspected for possible ligand-protein interactions that may influence selective binding to GluK1 or GluK3 receptors. Based on the computational outcome, a group of quinoxalin-2,3-diones was selected for further investigation and a method of their synthesis was developed.

**Acknowledgements**

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# NOVEL CYSTEINE-TARGETING INHIBITORS OF BACTERIAL UREASE

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Various species of microorganisms, such as *Helicobacter pylori* or *Proteus mirabilis* are able to colonize human organism thanks to their ureolytic activity. The damaging effect to host organism results from alkalization of pathogens environment due to ammonia release from urea molecules. The growing bacterial resistance to antimicrobial agents has stimulated studies on urease inhibition as a way to control colonization with *Helicobacter pylori* and *Proteus mirabilis.* Many phosphonic and phosphinic derivatives are known to tightly bind the active metallocenter of the biocatalyst. In this work, we acquired highly purified microbiological urease from *Sporosarcina pasteurii* using the techniques of column chromatography in ÄKTA Prime system. Using this enzyme, various unsaturated phosphonates were screened as potential slow-binding, covalent urease inhibitors. This group of compounds may show reactivity to thiol groups in cysteine residues that are located in the active site of the enzyme (apart from affecting the metallocenter). The most active of them may be considered promising therapeutic agents in the treatment of infections caused by ureolytic microorganisms. Results of the research suggest that most of the assayed compounds are slow-binding, competitive inhibitors. Several of them are characterized by $K_i$ value lower than 10 μM (respectively: 3,07 μM; 1,26 μM; 7,42 μM). They may be referenced to one of the most popular urease inhibitors – acetohydroxamic acid (AHA), which exhibited $K_i$ value of 5,36 μM under the reaction conditions.

# OPTIMIZATION AND DEVELOPMENT OF A NOVEL CLASS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) GAMMA LIGAND AS AN ANTICANCER AGENT

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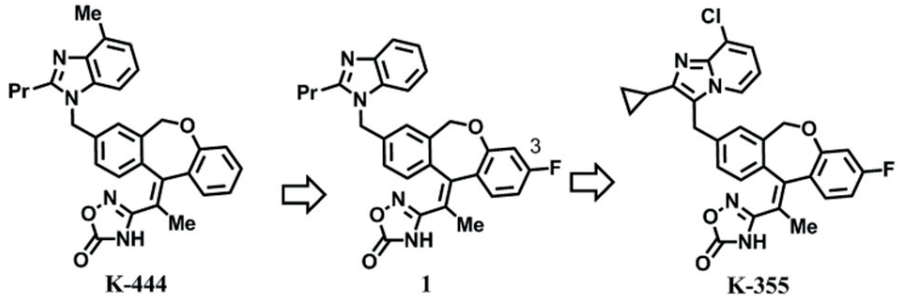
A PPARγ full agonist efatutazone has been developed as an anti-cancer drug candidate having potent cancer differentiation-inducing activity. PPARγ full agonists, however, including efatutazone showed adverse effects such as fluid retention probably due to thiazolidinedione (TZD) skeleton. We have reported discovery of new PPARγ ligand **K-444**. Since the scaffold of **K-444** is not TZD but dibenzooxepine and shows unique binding mode to PPARγ,[1] the optimization of **K-444** was carried out to develop the ligand without severe fluid retention.

Although **K-444** exerted remarkably potent MKN-45 gastric cancer cells aggregation activity, an indicator of cancer differentiation-inducing activity, its poor metabolic stability in human microsome was problematic. To this end, we identified the metabolically susceptible site via the analysis of **K-444** metabolites, and successfully discovered 3-fluoro dibenzooxepien derivative **1** having better human metabolic stability. Since the oxadiazolone moiety and the tricyclic core structure of **1** were essential for PPARγ agonistic activity, we then conducted the optimization of benzimidazole ring to afford better PK profiles for clinical studies. This found imidazo[1,2-*a*]pyridine derivatives **K-355**, which maintained potent MKN-45 gastric cancer cells aggregation activity and had better PK profiles than those of **1**. **K-355** exerted antitumor activity in AsPC-1 pancreatic cancer cells xenotransplanted mice, furthermore decrease of hematocrit in healthy BALB/C was tolerable even at 500 mg/kg, which was approximately 20 times higher than minimum effective dose in AsPC-1 xenograft model. This suggests that **K-355** is a promising candidate as anticancer agent with novel property.

Development of **K-355** from the lead compound **K-444**




**K-444** **1** **K-355**

| | K-444 | 1 | K-355 |
|---|---|---|---|
| HEK293 reporter $EC_{50}$ (nM) | 2.4 | 7.4 | 4.2 |
| MKN-45 aggregation $EC_{50}$ (nM) | 3.3 | 1.1 | 2.6 |
| $hCL_{int}$ (L/h/kg) | >24.9 | 3.2 | 2.2 |
| AUC (ng·h/mL) | N.T. | 1480 | 6890 |

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# HPH-15 HEALS EXPERIMENTAL SKIN FIBROSIS BY BLOCKING TGF-β/SMAD SIGNALING

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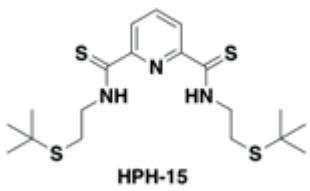
Transforming Growth Factor (TGF-β)/Smad signaling is well known to play a critical role in the pathogenesis of Systemic Sclerosis (SSc), which is an autoimmune disorder of unknown etiology. Activated fibroblasts and α-smooth muscle actin (α-SMA)-positive myofibroblasts are largely responsible for excessive matrix synthesis at the affected organs and identified as the pathological hallmark of SSc. Blockade of TGF-β signaling has been shown to reduce the development of skin fibrosis in several other experimental models but a molecule-based approach targeting TGF-β cascade has not been established yet.

To address this problem, we have synthesized a histidine-based small molecule, HPH-15, which has shown novel antifibrotic activity in several cell lines along with other potentials. In this study we have investigated HPH-15's antifibrotic effects in both mouse model and human dermal fibroblasts.




HPH-15

The effect of HPH-15 on the expression of extracellular matrix components and TGF-β signaling was demonstrated using human dermal fibroblasts in vitro. To examine in vivo antifibrotic effect of HPH-15, bleomycin-induced skin fibrosis model mice were deployed at two different oral administration onsets.

The study has revealed that HPH-15 suppresses the TGF-β induced phosphorylation of Smad3 and inhibits the expression of collagen 1, fibronectin 1, connective tissue growth factor, and α-smooth muscle actin induced by TGF-β in cultured human skin fibroblasts. In the bleomycin-induced model it has shown to be preventive against development of skin fibrosis as well as has ameliorated the already established one. Furthermore HPH-15 has suppressed the phosphorylation of Smad3 in various cells, including macrophages in the bleomycin injected skin. Additionally in the treated mice, dermal infiltration of proinflammatory macrophages ($CD11b^{+}Ly6C^{hi}$) and M2 profibrotic macrophages ($CD11b^{+}CD204^{+}$or $CD11B^{+}CD206^{+}$) was significantly decreased during the early and late stages, respectively. HPH-15 also resulted in decreased messenger RNA expression of the M2 macrophage markers arginase 1 and *Ym-1* in the skin, whereas it inversely augmented expression of Friend leukemia integration 1 and Krüppel-like factor 5 mRNAs, the transcription factor that repress collagen synthesis.

HPH-15 showed promising activity to inhibit skin fibrosis by occluding TGF-β/Smad signaling pathway. These results impart numerous positive qualities of HPH-15, including oral bioavailability and a good safety profile along with in vivo therapeutic effectiveness. Hence this small molecule (HPH-15) stands out as a potential TGF-β/Smad inhibitor candidate for SSc clinical trials.

# LIGAND-BASED DRUG DESIGN AND BIOLOGICAL EVALUATION OF NOVEL PROTEASOME INHIBITORS WITH INTEREST IN TRYPANOSOMIASIS

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Recent data indicate that approximately 6 to 7 million people in the world are infected by the protozoan Trypanosoma cruzi, responsible for the Chagas' disease, with most of them being found in Latin America.[1] From the family of trypanosomatids, there is also the protozoan of the genre Leishmania, which causes Leishmaniasis. With approximately 20 known species, all are capable of infecting mammals, most of which are responsible for the development of the disease in humans.[2] Although only a small fraction of people infected with this protozoan develop the disease, an estimated 700,000 to 1 million new cases and 20,000 to 30,000 deaths occur each year worldwide.[3]

Even with such impressive data, investment in discoveries of new drugs for the treatment of Leishmaniasis, for example, has been insignificant.[4] Even today, the first-line drugs used in the treatment of this disease have been discovered more than 50 years ago (antimonials pentavalents). Second-line drugs include pentamidine, a bactericide used to treat pneumonia, amphotericin B, which is an antifungal, and miltefosine, developed as an anticancer drug.[4,5]

Rational design of new drugs is thus stimulated and, especially for those with anti-trypanosomatid action, it is favored by the fact that the cellular organization of these protozoa is not the same in relation to the mammals and, consequently, the biological pathways of both are different.[6] This advantage can be explored for the discovery of new protozoan biological targets, for example: kinetoplastids DNA replication mechanism, protein transporters, cell cycle, proteasome and proteases.[6]

A relatively recent study published by Khare and Nagle [7] shows the proteasome of the species L. donovani, T. cruzi and T. brucei as a potential biological target. Accordingly, inhibition of the proteasome interferes with the orderly degradation of the cell cycle proteins, resulting in programmed cell death (apoptosis).[8] During the screening of low molecular weight compounds with kinetoplast proteasome inhibitory effect, Kare and Nagle identified as a hit the compound so called **GNF5343**. From this hit, modifications were made in its structure, aiming to improve potency and bioavailability of the new inhibitor, obtaining the compound so called **GNF6702**.

In this work, and with the aim of expanding the known chemical space of proteasome inhibitors, and specifically of kinetoplastídeos, virtual screening experiments were carried out on databases of commercially available compounds, based on the similarity of shape and electrostatic to **GNF6702**. Ten compounds were purchased and tested with intracellular amastigotes of T. cruzi, L. infantum and L. braziliensis. Results obtained revealed a natural compound that, in combination with the reference drug, benznidazole, presented results of higher activity and lower toxicity than benznidazole alone, whereas others of these compounds showed promising leishmanicidal activity, signaling that they should act by the same molecular mechanism of drug action, with interest for future trypanosomiasis treatment.

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# PLEIOTROPIC PRODRUGS: COVALENT INHIBITION OF ACHE AND ACTIVATION OF 5-HT4 RECEPTOR TO TREAT ALZHEIMER'S DISEASE

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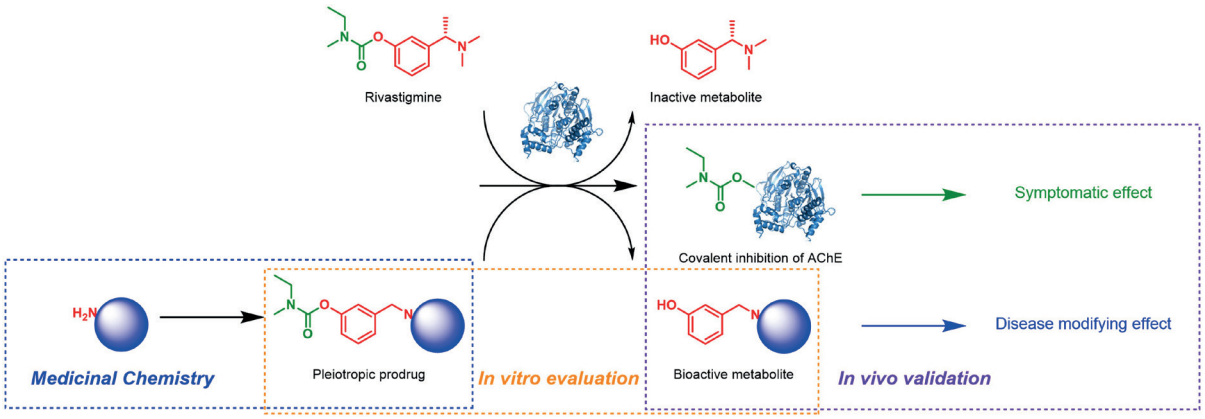
In 1906, Alois Alzheimer described the eponymous disease for the first time from the observation of his patient who suffering from particular memory disorders and presented brain pathologic deposits. A century after this discovery and in order to treat Alzheimer's disease, a lot of molecules have been developed but only 4 are currently marketed. They are mostly acetylcholinesterase inhibitors (AChE), as for rivastigmine a covalent pseudo-irreversible inhibitor. These treatments are purely symptomatic and permit temporary restoration of the cholinergic neurotransmission impaired by the neurodegeneration.[1]

Facing the complexity of the disease and the lack of effectiveness of the current molecules, we have developed multi-target directed ligands as new strategy, which consist in drugs with several therapeutic targets of interest to treat a disease.[2] For example, our laboratory synthesized Donecopride a molecule inhibiting AChE and simultaneously activating 5-$HT_4$ serotoninergic receptors.[3]

My project consists in the development, the synthesis and the biological evaluation of new innovative molecules with novel mechanism: pleiotropic prodrugs. Thanks to their structural analogy with rivastigmine, our candidates will covalently inhibit AChE, allowing to release an active metabolite on serotonin 5-$HT_4$ receptors, a target of choice in this disease.

This communication will detail the synthesis of various prodrugs, their *in vitro* evaluation and *in vivo* validation. The notion of pleiotropic prodrugs will be explained in more details.

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# STEREOSELECTIVE SYNTHESIS AND BIOLOGICAL EVALUATIONS OF RVD1N-3 DPA

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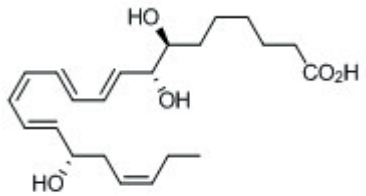
Specialized pro-resolving mediators (SPMs) display very potent anti-inflammatory and pro-resolving agonists effects towards G protein-coupled receptors (GPRs).[1] The resolution of inflammation is now recognized to be an active process strictly regulated by individual families of SPMs and is therefore seen as a biomedical paradigm shift.[2] SPMs are stereoselectively biosynthesized from ω-3 polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and docosapentaenoic acid (n-3 DPA), in the presence of lipoxygenases and cyclooxygenase-2.[1]

The first total synthesis of the specialized pro-resolving mediator $RvD1_{n\text{-}3\ DPA}$[3] has been achieved using the underutilized $sp^3$-$sp^3$ Negishi cross coupling reaction and an alkyne hydrosilylation-protodesilylation protocol. The LC-MS/MS results of the synthetic material matched those of endogenously produced $RvD1_{n\text{-}3\ DPA}$ allowing assignment of the absolute configuration of this lipid mediator. Biological evaluations revealed that this novel mediator displays low nanomolar pro-resolving properties in vivo and potently activates the GPR32 receptor. As such, this natural product is of interest as a lead compound towards developing novel immunoresolvents as putative new anti-inflammatory drugs.[2,4]




$RvD1_{n\text{-}3\ DPA}$

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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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# HINT1: A POTENTIAL NON-OPIOID TARGET FOR PAIN

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Over 100 million Americans suffer a significant decrease in their quality of life and productivity due to chronic pain.[1] Consequently, there is an increasing demand for the development of new approaches for the treatment of pain.

Through the use of medicinal chemistry, biochemistry and neuropharmacology studies, our team has recently demonstrated that Histidine Triad Nucleotide Binding Protein 1 (HINT1) is a key mediator of the cross-regulation of the μ-opioid receptor (MOR) and the glutamatergic N-Methyl-D-Aspartate Receptor (NMDAR).[2] The ability of MOR activation to reduce pain is highly dependent on its interaction with NMDAR. We have found that HINT1 directs the association of MOR with NMDAR. Upon binding with morphine and activation of analgesia, Zn is mobilized and binds to the HINT1 active site, resulting in Protein Kinase C gamma (PKCg) recruitment. NMDAR phosphorylation by PKCg results in activation of the channel and Calmodulin-Dependent Kinase II (CaMKII) suppression of MOR. [2] Consistent with these observations, HINT1 knock-out mice exhibited enhanced analgesia and resistance to tolerance with no apparent adverse side-effects.

Through kinetic, mutagenic and x-ray crystallography studies, our group has delineated key features of the catalytic mechanism and potential biochemical role of human HINT1. These studies have enabled the rational design of inhibitors of hHINT1. We have demonstrated that the dosing of mice with one of these inhibitors, 5'-tryptamine guanosine carbamate (TpGc), can significantly enhance morphine analgesia, reverse morphine tolerance and reduce neuropathic pain.[3] In addition, we have also recently demonstrated that TpGc can abolish chemotherapeutic induced neuropathic pain, as well as block the antagonist effect of the mu-opioid receptor on NMDAR activation in the spinal cord. Taken together, our results demonstrate the unique regulatory role of HINT1 on MOR and NMDAR, as well as reveal it to be a potential new non-opioid target for the development of pain therapeutics. The results of ongoing mechanistic and chemical probe development studies will also be discussed.

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# 5-SUBSTITUTED-2-THIAZOL-4-n-PROPYLPIPERAZINES AS NON-IMIDAZOLE HISTAMINE H3 RECEPTOR ANTAGONIST: FURTHER STRUCTURE-ACTIVITY RELATIONSHIP EXPLORATION AND IN VITRO AND IN VIVO PHARMACOLOGICAL EVALUATION

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Our previous study described two series of *N*-methyl-2-[2-(4-propylpiperazin-1-yl)-1,3-thiazol-5-yl]- [1] and *N*-methyl-2-[2-(4-propylpiperazin-1-yl)-1,3-thiazol-4-yl]ethan-1-amine derivatives [2] in which the terminal secondary *N*-methylamino function has been substituted with ω-aliphatic and ω-phenylaliphatic moieties with a moderate to pronounced affinity for the histamine $H_3$ receptor. It was shown by comparison of the homologous pairs of both series, that the presence of the aforementioned substituents at position 5 in the thiazole ring is favorable for histamine $H_3$ receptor antagonist activity, whereas substitution at position 4 typically leads to a strong decrease of activity. The highest affinity for these series was seen for the derivative bearing *N*-methyl-*N*-phenylpropyl moiety (**ADS-531)** [1]**.** Therefore, **ADS-531**, which did not exhibit any $H_1$-antagonistic activity, was chosen as the lead compound for further structural modification.

The aim of the present study was, hence, to optimize the structure of the lead compound **ADS-531**. To this end, a series of 5-substituted-2-thiazol-4-*n*-propylpiperazines were synthesized and their pharmacological properties functionally evaluated with an *in vitro* test system using guinea pig jejunum preparations. In this series, the alkyl chain between position 2 of the thiazole ring and the terminal secondary *N*-methylamino function was elongated from three to four methylene groups. The *N*-methylamino group was substituted by benzyl-, 2-phenylethyl-, and 3-phenylpropyl- substituents, these substituents being found to have the highest potency in the previously described series of thiazoles [1]. Furthermore, compounds with the highest potency at the $H_3$ receptor were also tested for $H_1$ antagonistic effects *in vitro*, according to standard methods, using guinea pig ileum.

The results of SARs, together with previously described data, indicated that compound **ADS-531** was the most active compound that we have so far synthesized in this series. This compound was evaluated for its affinity for the recombinant rat and human histamine $H_3$ receptors ($rH_3R$ and $hH_3R$, respectively), transiently expressed in HEK-293T cells. Additionally, derivative **ADS-531** was subjected to *in vivo* evaluation of its impact on feeding behavior and brain neurotransmitter systems after repeated peripheral administration to rats. Postmortem analyses of the rat brain tissues were also carried out to determine the activities of MAO-A, MAO-B, and HNMT.

In competition radioligand binding studies at the rat histamine $H_3$ receptor, compound **ADS-531** showed slightly lower nanomolar affinity than the reference compound – thioperamide, and slightly higher than histamine. Significantly higher affinity was observed for **ADS-531** at the human $H_3R$ than thioperamide and histamine. **ADS-531** given parenterally for five days did not influence the food intake in rats. No significant changes were observed in histamine concentration, nor in the enzyme activities related to histamine metabolism examined in the brain. The apparent lack of the effects of the tested compound on the histaminergic system was by no means caused by the lack of its ability to cross the blood-brain barrier. The presented data leaves no doubt that **ADS-531** caused alterations in the concentrations of dopamine, noradrenaline, and serotonin.

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# TARGETING SEROTONINERGIC SYSTEM, CHOLINESTERASES AND AMYLOID-BETA AGGREGATION IN THE SEARCH FOR EFFECTIVE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disorder caused by a combination of pathological processes including aggregation of amyloid-β (Aβ) and neurofibrillary tangles, oxidative stress and inflammation, leading ultimately to neuronal cell death [1]. Currently available anti-AD drugs, developed on the one-target one-drug paradigm, are used to maintain neurotransmission, but they do not stop or reverse the progression of the disease. It is accepted that complex diseases, like AD, require multi-target (multifunctional) drugs for effective treatment. Such multi-target drugs are able to interfere with several pathological processes at the same time. Selection of appropriate combination of biological targets is crucial for the effectiveness of the new multifunctional compounds.

Based on the current knowledge and results of preclinical and clinical trials, in our project we have selected cholinesterases, 5-HT6 receptors and Aβ as biological targets of key importance for the development of AD and therefore for the treatment [2]. Previously, we have developed the first series of 5-HT6 receptor antagonists endowed with cholinesterase inhibitory activity and Aβ anti-aggregating properties [3]. The compounds showed a unique pharmacological profile in vitro and in vivo, however, their physicochemical and pharmacokinetic properties needed to be improved (compound I, Figure 1). Herein we present design, synthesis and biological evaluation of a new set of compounds with improved drug-like properties and multifunctional profile promising for the development of new anti-AD therapeutics.

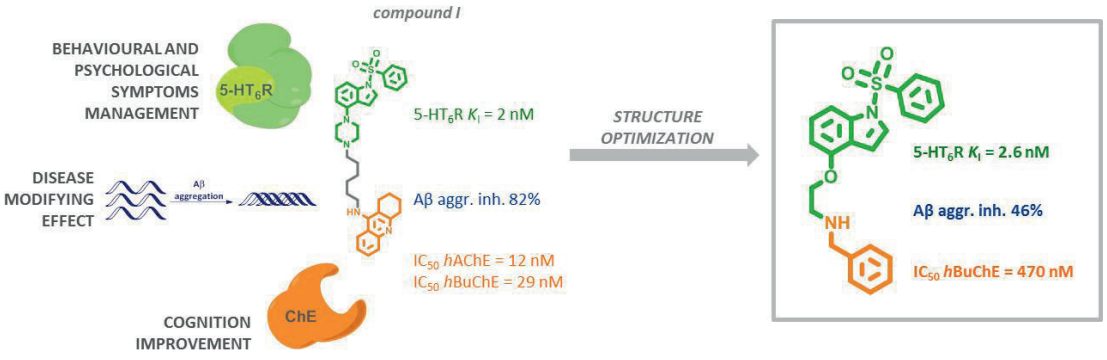


**Figure 1.** Design of new multifunctional ligands based on disease-modifying and symptomatic biological targets

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# BIOLOGICAL ACTIVITY OF NEW DERIVATIVES OF QUINAZOLIN-2-ONE

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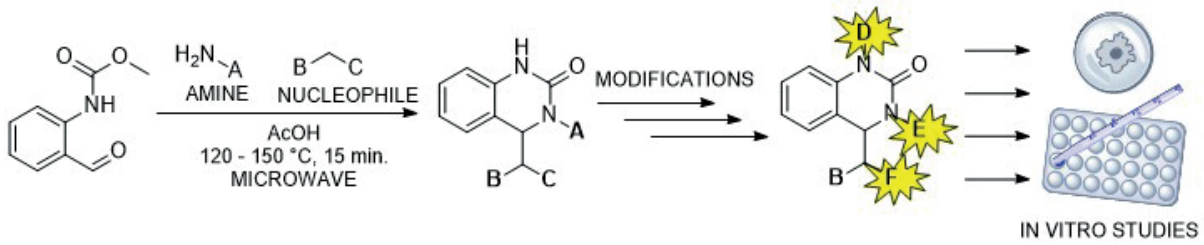
Quinazoline- and quinazolinone-derivatives constitute an important group of pharmacologicaly-active compounds. As inhibitors of enzymes and receptor ligands they have been investigated for decades and found application in treatment of various prevalent diseases (e.g. doxazosin, methaqualone, erlotinib) [1].

The work described herein is a continuation of chemical and pharmacological studies in the group of derivatives of 3,4-dihydroquinazolin-2(1H) –one with potential biological activity. [2-4] The aim of the project was to obtain a series of new 3,4-dihydroquinazolin-2(1H)-one (1,2,3,4-tetrahydroquinazolin-2-one) derivatives for the purpose of chemical and biological studies. As the main method of synthesis, facile, fast and environmentally-friendly microwave-assistedthree-component cyclisation was applied. [2-4] Considering the simplicity of the method and the functional group compatibility (e.g. EWG, carbonyl) this transformation has proven useful in medicinal chemistry projects - as a source of easily-accessible building blocks or final structures.




Using different amines and nucleophiles a series of various 3- and 4-substituted 3,4-dihydro-1H-quinazolin-2-ones was obtained in good yields. The use of “new” types of nucleophiles allowed us to obtain a new types of substitution in position 4 (including e.g. nitrille, phthalimide or barbituric acid). Several of the obtained compounds were used as intermediates for further modifications (e.g. Huisgen 1,3-dipolar cycloaddition).

The obtained derivatives were tested in several in vitro assays evaluating their inhibitory potency against different enzymes, affinity to receptors and metal chelating or antioxidant capacity.

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# INHIBITION OF THE G-PROTEIN-COUPLED RECEPTOR GPR55 PREVENTS PANCREATIC TUMOR GROWTH VIA REDUCED YAP SIGNALING

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**Background and Purpose**: GPR55 is a G-protein-coupled receptor that primarily signals through $Ga_{12,13}$ and $Ga_q$ proteins to promote cancer cell proliferation and targeting GPR55 offers anti-cancer protection against various cancer cell types. We aimed to assess the potency and mechanism of action of the GPR55 inhibitor, (*R*,*S'*)-4'-methoxy-1-naphthylfenoterol [(*R*,*S'*)-MNF], in pancreatic cancer.

**Experimental Approach**: *In vitro* assays of cell proliferation, signal transduction, and protein expression were performed in PANC-1 pancreatic cancer cells. A nude mouse PANC-1 xenograft model was generated to study the effect of (*R,S'*)-MNF on tumor growth *in vivo*, and tumor tissues were analyzed using multiplatform non-targeted and targeted metabolomics, global RNA microarray, and Western immunoblotting.

**Key Results**: (*R*,*S'*)-MNF significantly inhibited cell proliferation and blocked GPR55-mediated ERK activation. The reduction in PANC-1 tumor growth by (*R*,*S'*)-MNF was associated with altered lipid metabolism and metabolic reprogramming. Targeted metabolomics validated metabolome changes in cysteine/methionine metabolism and associated oxidative stress, protein degradation, and pyrimidine nucleotide synthesis. Transcriptomics analysis of (*R*,*S'*)-MNF-treated PANC-1 xenograft tumors revealed a downmodulation of genes involved in Hippo/YAP and Wnt/b-catenin pathways, coinciding with reduced expression of YAP, b-catenin, HIF-1a, and c-Myc proteins.

**Conclusion and Implications:** The growth and metastasis of pancreatic cancer has been previously linked to upstream signals that regulate the YAP/TAZ pathway. Here, we provide evidence of the contribution of YAP/TAZ and Wnt signaling pathways in the pro-oncogenic activity of GPR55 and ultimately into the mechanisms that drive tumorigenesis. The ability of (*R*,*S'*)-MNF to inhibit GPR55 may represent a novel anti-cancer treatment.

# THIOCYANATES AS A NEW CLASS OF SELECTOVE SIRT1 INHIBITORS

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Sirtuins are class III histone deacetylases (HDACs)[1] that, unlike other HDACs, are not Zinc-dependent but use NAD+ as a cofactor to cleave off various different acyl groups from the ε-amino residues of lysines.[2] Through their great range of substrates they influence various cellular processes like metabolism, stress response, DNA repair, cell survival or apoptosis.[3] Therefore sirtuins are associated with the pathogenesis of various diseases, like cancer, metabolic or neurodegenerative diseases.[4] Of the seven human sirtuin isotypes Sirt1 is the most extensively studied one. It is linked to aging in general and specifically to age related diseases, like for example Alzheimer`s or Huntington`s Disease (HD). The first Sirt1 inhibitor to pass phase I and II clinical studies, Selisistat is currently examined in a phase III trial for treatment of HD.[5] More modulators of Sirt1 are needed to exploit and further characterize its therapeutic use.

We tested a small library of commercially available compounds proposed by docking studies against Sirt1, 2 and 3. OSSK 221646 was found to selectively inhibit Sirt1 with an IC50 of 13.0 ± 0.6 µM. Analogues showed that the thiocyanate structure of the compound was key to the selectivity and high affinity towards Sirt1. To enable cellular studies new analogues of the thiocyanates with higher solubility were identified through docking studies and tested. Compounds that showed micromolar IC50 values *in vitro* were further studied in cells. Therefore levels of γH2AX, which are lower in Sirt1 KO cells than in WT, were examined.[6] We obtained similar protein levels of γH2AX for Sirt1 KO cells as well as cells treated with Selisistat or the thiocyanates. These results show that thiocyanates are a promising new class of selective Sirt1 inhibitors.

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# OPTIMIZATION AND DEVELOPMENT OF NOVEL CLASS PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) GAMMA LIGANDS AS ANTICANCER AGENTS

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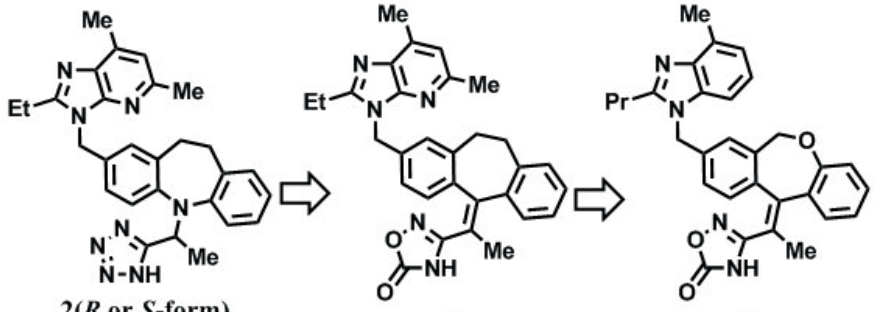
Peroxisome proliferator-activated receptor (PPAR) γ full agonist efatutazone is expected as an anti-cancer agent having differentiation-inducing effect on cancer cells which is different from the conventional agent. However, side effects of existing PPARγ full agonists such as fluid retention, which are thought to be attributed to thiazolidinedione structures, have hampered their approval. We started discovery research based on the hypothesis that PPARγ agonists with a novel scaffold and receptor binding mode would be able to avoid the side effects.

Through our HTS campaign with PPARγ reporter gene assay, dibenzoazepine derivative **1** (*R* or *S* isomer) with potent PPARγ agonistic activity was obtained. Due to the existence of the asymmetric center adjacent to the nitrogen atom on the azepine ring, the drug design of an alternative scaffold avoiding a chiral center was conducted to enable the efficient optimization of the core structure and imidazopyridine of hit compound **1**[1]. As a result of the conformational search of model substrates **(*R*)-1'** and **(*S*)-1'** using molecular modeling tool MacroModel, interestingly, olefinic *E/Z* isomers **2** and **3** mimic dibenzoazepine core structure, which was flipped due to chiral structure of **1'**. Dihydrodibenzocycloheptene derivative **4**, which was reflected the result of the conformational studies, maintained the reporter activity compared to **1**. Thus, we succeeded in the effective scaffold-hopping (Table 1).

Furthermore, **5**, which was optimized the imidazopyridine part and the scaffold, showed potent PPARγ agonistic activity, and induced the differentiation of MKN-45 cells at same concentration range. Since this compound showed poor metabolic stability, we conducted the blockade of the main oxidative metabolism site by the introduction of fluorine and also optimized the benzimidazole ring. This lead to the promising compound **K-928**. **K-928** exerted antitumor activity against poorly differentiated cancer cells xenotransplanted into mice. These data suggest that this compound may become a new candidate for treatment of cancers.




2(*R* or *S*-form)
(-)-form 86%ee

3

1

| | 2 | 3 | 1 |
|---|---|---|---|
| HEK293 reporter $EC_{50}$ (nM) | 197 | 177 | 2.4 |
| MKN-45 aggregation $EC_{50}$ (nM) | N.T. | N.T. | 3.3 |

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# DISCOVERY OF DIBENZOOXEPINE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) GAMMA LIGANDS HAVING A NOVEL BINDING MODE FOR ANTICANCER AGENTS : EFFECTIVE MIMICRY OF CHIRAL STRUCTURE BY OLEFINIC E/Z ISOMERS

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Efatutazone, peroxisome proliferator-activated receptor (PPAR) γ full agonist, is expected to be an anti-cancer agent having unique differentiation-inducing effects on cancer cells. However, common side effects of PPARγ full agonists (eg. fluid retention), probably derived from thiazolidinedione (TZD) skeleton, have hampered their development. Therefore, we sought to find PPARγ agonists with a scaffold other than TZD and different receptor binding mode, which would avoid the side effects.

Throughout HTS campaign with PPARγ reporter gene assay, dibenzoazepine compound **1** was obtained as a hit. Initial optimization of **1** led to the discovery of compound **2**, which exerted more potent PPARγ agonistic activity. To perform the optimization of the core structure and imidazopyridine moiety of **2** efficiently, elimination of the asymmetric center was conducted.[1)] The conformational search of model substrates of **2** using the molecular modeling tool MacroModel showed conformation of (*R*)-**2'** was likely to be restricted due to the steric effect of methyl group attached to chiral center and the stable conformation of (*R*)-**2'** would overlap that of the olefinic compound **3**. Actually, dibenzooxepine derivative **4**, synthesized based on the conformational studies, showed more potent reporter activity, indicating successful scaffold hopping.

Dibenzooxepine derivative **4** showed significant PPARγ agonistic activity, and certainly had a different binding mode to PPARγ from those of known PPARγ agonists.Expectedly, **4** also induced the differentiation of MKN-45 gastric cancer cells at the same concentration range as reporter assay.

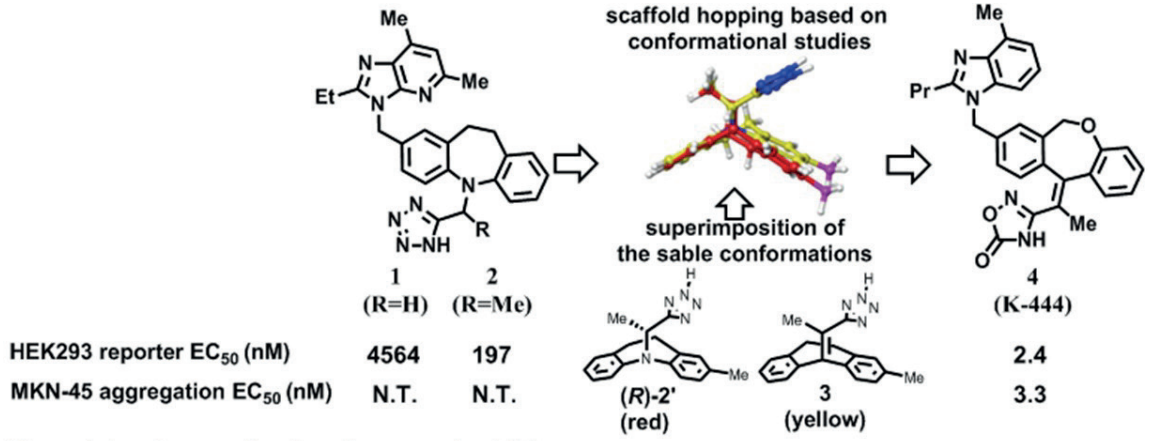


Figure 1. Lead generation from the screening hit **1**.

1) Yamamoto, K. *et al.*, *J. Med. Chem.* **2018**, *61*, 10067-10083.

# IMIDAZOPYRIDINE-BASED 5-HT6 RECEPTOR MODULATORS WITH UNIQUE IN VITRO PHARMACOLOGICAL PROPERTIES: A DIFFERENT IMPACT OF N1-BENZYL AND N1-PHENYLSULFONYL FRAGMENT ON RECEPTOR FUNCTIONAL ACTIVITY

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The 5-hydroxytryptamine type 6 receptor (5-$HT_6$R) belongs to the superfamily of G protein-coupled receptors (GPCRs) positively coupled with adenylyl cyclase [1]. Apart from this well-established signaling pathway, 5-$HT_6$R engages the mammalian target of rapamycin (mTOR) as well as recruits cyclin-dependent kinase 5 (Cdk5) and thus controls learning, memory and neurodevelopment processes. Another important feature of 5-$HT_6$R, which depends on its association with interacting partners, is its high level of constitutive activity [2].

We have recently applied a scaffold-hopping approach to design a focused library of $N_1$-benzyl and $N_1$-phenylsulfonyl derivatives of 3*H*-imidazo[4,5-*b*] and 1*H*-imidazo[4,5-*c*]pyridines as novel 5-$HT_6$R modulators. The study allowed the identification of compound PZ-1444 bearing the $N_1$-benzyl moiety, which behaved as 5-$HT_6$R partial inverse agonist in $G_s$-mediated signalling pathway ($K_i$ = 6 nM, $IC_{50}$ = 17.6 nM) [3]. In parallel study compound PZ-1727 containing $N_1$-arylsulfonyl fragment, was classified as 5-$HT_6$R neutral antagonist in $G_s$ signalling ($K_i$=1 nM, $IC_{50}$ = 5.4 nM). Both compounds did not affect the neural differentiation in NG108-15 cells mediated by 5-$HT_6$R-elicted Cdk5 activity.
Compound PZ-1727 showed interesting glioprotective properties by reducing the doxorubicin-induced cytotoxicity on astrocytes in the MTT test. In contrast, compound PZ-1444 and intepirdine, both classified as inverse agonist, displayed no glioprotecting properties in this test.

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# 8-BENZYLAMINOXANTHINE DERIVATIVES AS DUAL-TARGET A1/A2A ADENOSINE RECEPTOR ANTAGONISTS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

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Neurodegeneration is characterized by a progressive loss of neurons leading to central nervous system dysfunction. The main clinical manifestations of neurodegenerative diseases (NDs) can be divided into movement disorders (Parkinson disease, PD) or mental functioning impairment (Alzheimer disease, AD). [1] The management of multifactorial NDs is a challenge for current medicinal chemistry due to the wide spectrum of potential biological targets without any single molecular mechanism targeting all biochemical aspects. Therefore, the multi-target-directed ligand (MTDL) approach has been proposed as a promising strategy. [2]

In the current study, we have explored a new chemical library of compounds derived from 8-benzylamino- and 8-benzyloxy-xanthine in the search for potent and well-balanced dual $A_1/A_{2A}$ adenosine receptor (AR) antagonists. The proposed dual active compounds may provide symptomatic and disease-modifying effect.[3]

The investigated compound library includes structures with various substituents on the aromatic residue as well as at position *N*1, *N*3 and *N*7 of the xanthine core. The synthetic protocol leading to the final xanthine derivatives was developed based on a modified Traube procedure and our recently published methodology.[4] The obtained compounds were tested in radioligand binding assays to determine affinity for human $A_1$AR, $A_{2A}$AR, $A_{2B}$AR and $A_3$ARs expressed in Chinese hamster ovary (CHO) cell membranes.The performed structure-activity relationship analysis provided insights into the structural requirement for both biological targets.

As a result of our efforts, we identified potent dual active structures (MZ-1490; $A_1$: 130 nM; $A_{2A}$: 61 nM) as well as selective $A_{2A}$ adenosine receptor antagonists (JS-16029; $A_1$: >1000; $A_{2A}$: 71 nM). The promising preliminary outcomes warrant further investigation within the presented series of xanthine derivatives including studies of toxicity and neuroprotection.

**Acknowledgements**

Financial support by the National Science Center grant based on decision No DEC-2016/23/N/NZ7/00475 and Jagiellonian University Medical College grant K/ZDS/007121 are gratefully acknowledged.

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# INVESTIGATING MT5-MMP, A NEW POTENTIAL RELEVANT TARGET FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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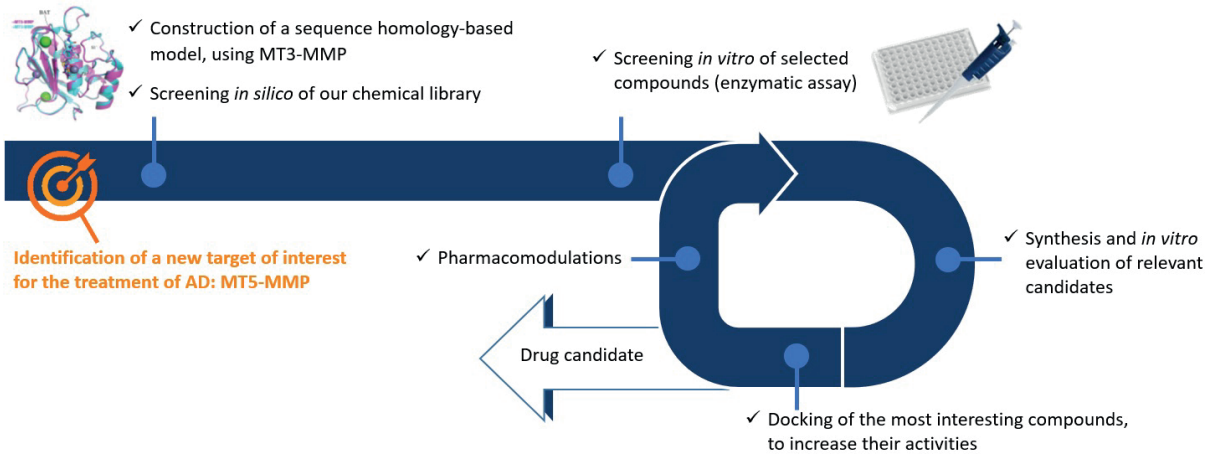
In 2018, the number of people living with dementia in the world is estimated at **50 million** and Alzheimer's disease (AD) is the most common form of **dementia**. AD is a **neurodegenerative** and **incurable** brain disorder; only treatments for symptoms are available at this time. Because of the heavy economic and societal impacts, there is an urgent need to find new treatments that target the molecular causes of neuronal cell death.

Two abnormal structures in the brain called **β-amyloid (Aβ)-containing plaques** and **neurofibrillary tangles** are considered as two of the main features of AD. In this context, several studies support the hypothesis that alterations in the processing of amyloid precursor protein (APP), resulting in the accumulation of β-amyloid peptides (Aβ) and other proteolytic products contributes to AD pathogenesis. Thus, current research focuses on the enzymes involved in APP cleavage such as α-, β-, and γ-secretases. However, recent studies have revealed the existence of **another physiological APP processing pathway**, mediated by a novel AD-related enzyme, membrane-type 5-matrix metalloproteinase (**MT5-MMP**), that can **process APP** and **promote Aβ** and **CTFβ accumulation**, as well as the **inflammatory** process in AD transgenic mice.[(a),(b),(c)] Moreover, MT5-MMP can cleave APP upstream from the β-secretase cleavage site (the so called **η-cleavage site**)[(d)] and release a *N* -terminally elongated Aβ fragment (**Aη-α**), which appears to be **synaptotoxic**.[(e)]

We aim to design and synthesize the first non-peptidic MT5-MMP inhibitor through an interdisciplinary approach including molecular modelling, medicinal chemistry and biology. Starting from a hit compound identified by *in silico* screening, we are now investigating the pharmacomodulations on that scaffold to gain in affinity and selectivity for MT5-MMP.

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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.

**Acknowledgments**
Prof. Zoidis would like to thank Gilead Hellas for the financial support (Asklepios Gilead Grants).

# AROMATIC BASIC GROUPS IN THE DESIGN AND SYNTHESIS OF SEROTONIN RECEPTOR LIGANDS

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Aminergic receptors (*i.e.*, G-protein coupled receptors activated by endogenous amines, classically serotonin, histamine, acetylcholine, catecholamines: dopamine, adrenalin, noradrenalin and trace amines) are the targets of ~25% of drugs. So far, a vast majority of ligands and almost all agonists of aminergic receptors were built around highly basic amine fragments, *e.g.* aminoalkyl chain, piperazine, pyrrolidine or other cyclic amines.
In contrast to the existing paradigm, amidine based aromatic heterocycles emerge as a new, non-classical, aminergic GPCR binding chemotype.[1-3] A recently described, 1-alkylimidazole based series of 5-$HT_7$R agonists is the first example of low-basicity serotonin receptor agonists, while the weakly basic 2-aminoimidazole and other cyclic amidine derivatives exhibited remarkable affinity for the 5-$HT_6$ receptor and antagonistic function. Evidence coming from molecular modelling, potentiometric titration experiments and mutagenesis indicate a distinctive binding mode, which is different from classical ligands. Due to both resonance and induction, the amidine containing heterocycles can be finely tuned to meet the desired criteria of basicity, lipophilicity, while also keeping the right molecular shape, bulkiness etc.
The most prominent advantages of the compounds developed using the aforementioned strategy versus the classical highly basic scaffolds involves higher selectivity, lowered anti-target (*e.g.* hERG) binding, high water solubility, high 'tunability' and possibly improved blood-brain barrier permeation due to the domination of the unprotonated, *i.e.*, uncharged molecules in physiological pH solutions.

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# HOW TO RATIONALIZE HALOGEN SUBSTITUTION – CASE STUDY OF SEROTONIN RECEPTOR LIGANDS

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Most of the existing serotonin receptor ligands are based on tryptamine, arylpiperazine or phenylethylamine scaffolds,[1,2] but new structures are sought to expand the space of existing tool compounds and in consequence find better ones. Among existing 5-HTR ligands, the above mentioned chemotypes can be found in molecular probes such as 5-carboxytryptamine or LP-211.[3]
A relatively new approach is the rational use of halogens in the design of serotonin receptor ligands, in order to optimize the halogen bonding between the compound and the receptor. This interaction stems from anisotropy of charge density on the halogen atom. A properly located halogen can increase the affinity of the ligand severalfold.[3,4]

[2-(1*H*-indol-3-yl)ethyl][(1*H*-indol-3-yl)methyl]amine, an unsubstituted pilot compound possessing serotonergic activity served as a case study in our project.

The preffered positions of the halogen substitution in this scaffold were indicated using a QPLD/MM-GBSA protocol.[4] The subsequent synthesis involved the reductive amination reaction of a halogen-substituted indole containing synthons. Ligands with a broad serotonergic activity were obtained, while certain substitution patterns switched also the $D_2$ receptor activity.

This study was supported by the National Science Centre within grants SONATA 2014/15/D/NZ7/01782 and OPUS13 2017/25/B/NZ7/02929.

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# PREPARATION OF POLYMER-EMBEDDED GPR55 NANOPARTICLES: A PROMISING ANALYTICAL POSSIBILITY FOR GPCR IN-SOLUTION DRUG BINDING STUDIES

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GPR55 is a recently deorphanized lysophospholipid receptor (LPL-R) [1] which was reported to play an important role in inflammatory/neuropathic pain, metabolic disorder, bone development and it's use as an oncological molecular target. [2] Up to this point, cellular based pharmacological studies of GPR55 give largely inconsistent results. Development of the *in vitro* research platform for purified GPR55 could be beneficial in disclosing the cryptic nature of GPR55 pharmacology. This in turn, might open the path to the design and development of innovative therapeutic agents. One of the main obstacles in studying membrane receptors lays in the amphiphilic nature of transmembrane proteins (TMs) existing in a two highly chemically disparate environments, which means that obtaining water soluble homogenous solution of TMs is problematic. On top of that, it's now widely known that GPCRs rely on the interactions with other constituents of cell membrane like cholesterol and surrounding (annular) lipids. [3] Thus, it is very difficult to obtain both fully functional and water-soluble form of GPCRs to be used for drug binding studies in solution.

Recent advances in membrane protein research has allowed to develop new approaches for the solubilization of TMs inside fragments of native cell membrane surrounded by an amphiphilic polymer. The most described polymer for this application is the styrene-maleic acid co-polymer (SMA), which can be used to produce tailored polymer-embedded membrane nanoparticles called SMA lipid particles (SMALPs). [4]

This poster reports on the preliminary outcomes of a joint project that aims at the development and optimization of a protocol for the incorporation of GPR55 into native membrane nanoparticles. Tailor made recombinant version of appropriately tagged human GPR55 had to be engineered in order for the protein to be detectable and purifiable. Stably transfected HEK293T cells expressing human GPR55 protein were used for the study. Subsequently, the homogenate containing suspended membrane fractions was used for SMALP assembly by incubation with a commercial formulation of pre-hydrolyzed SMA. Analysis by size exclusion chromatography (SEC) and immunodetection allowed to prove the formation of GPR55-SMALPs directly from HEK293T cell membrane suspensions treated with SMA. Further purification steps encompassed immobilized metal affinity chromatography utilizing histidine tagging of the recombinant GPR55 receptor.

The presented technique has the potential to become a standard approach for drug binding studies on GPCRs by means of spectroscopic and biophysical methods, such as isothermal titration calorimetry, circular dichroism and surface plasmon resonance.

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# COMPUTATIONAL MODELING OF THE TAUTOMERIC INTERCONVERSIONS OF THE QUERCETIN MOLECULE

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Quercetin molecule (3, 3′, 4′, 5, 7-pentahydroxyflvanone, $C_{15}H_{10}O_7$) is an important flavonoid compound, which is found in many foods and plants, and is known to act as a natural drug molecule with a wide range of treatment properties, like an anti-oxidant, anti-toxic etc. Notably, that in the composition of the biologically-active compounds in natural conditions quercetin shows quite effective treatment properties, while in the extracted state this molecule shows more effective mechanism of action, however already with toxicological manifestations.

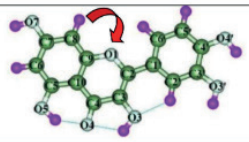
So, at the analysis of the pharmacological properties of the quercetin molecule it should be taking into account its possibility to acquire different tautomeric forms, ranging greatly by their energies.

In this study we revealed and investigated the possible pathways of the tautomeric transformations of the quercetin molecule, which potentially influence on its pharmacological and clinical effectivity (Scheme 1). Also, it was revealed that single proton transfer can induce cascade tautomeric reactions in the quercetin molecule.

These transformations of the quercetin molecule are accompanied by the rearrangement (breakage and formation) of the intramolecular H-bonds, changes of their geometry and dipole moment (value and direction).

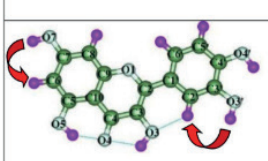
Obtained results can be useful for the formulation of the general rules of the formation and importance of tautomeric states, which can be applied to different heterocyclic molecules with potential biological or pharmaceutical activity.

**Transition of the proton atom to the neighboring oxygen atom O1**

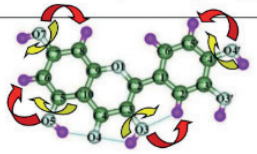


(1)

**Transition of the proton atom from the O7H/O3′H hydoxyl groups to the neighboring C6/C2′ carbon atoms (2) and from the O7H/O5H/O3H/O4′H hydoxyl groups to the C8/C6/C2′/C5′ carbon atoms, preceded by the rotations of the hydroxyl groups around the C7O7/C5O5/C3O3/C4′O4′ axis by 180 degree (3)**

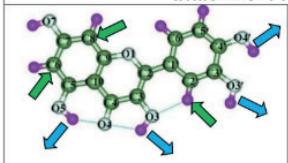


(2)



(3)

**Transition of the proton atom by its splitting from one sites and attachment to the other sites**



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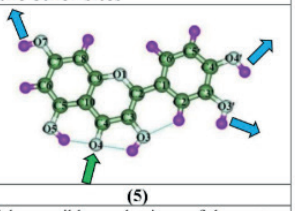

(5)

**Scheme 1.** Schematic representations of the possible mechanisms of the proton mobility inside the quercetin molecule, causing different tautomeric forms. Red arrows denote the directions of the intramolecular proton transfer, yellow – rotations o the hydroxyl groups by 180 degree, blue – sites of the proton splitting and green – sites of the proton attachment.

# ALCHEMICAL FREE ENERGY CALCULATIONS OF AMINOADAMANTANES BOUND TO THE CLOSED STATE OF INFLUENZA A/M2TM

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Adamantane derivatives, such as amantadine and rimantadine, have been reported to block the transmembrane domain (TM) of the M2 protein of influenza A virus (A/M2) but their clinical use has been discontinued due to evolved resistance in humans. Although experiments and simulations have provided adequate information about the binding interaction of amantadine or rimantadine to the M2 protein, methods for predicting binding affinities of whole series of M2 inhibitors have so far been scarcely applied. Here we show that alchemical free energy calculations of ligand binding using the free energy perturbation (FEP) method and the thermodynamic integration (TI) are valuable for determining the relative binding affinity of aminoadamantane derivatives against M2TM WT in 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) lipids to mimic the membrane environment. The binding affinities of 20 compounds were measured by isothermal titration calorimetry (ITC) against the A/M2TM WT tetramer in its closed form at pH 8 and used as experimental probes covering a binding affinity range of only ~ 2 kcal $mol^{-1}$. However, a fair correlation was found which demonstrates that binding free energy calculations can be used to predict relative binding affinities of aminoadamantane derivatives towards M2TM with good accuracy. Such methods could assist in the development of novel potent inhibitors that overcome A/M2 resistance.

# UNLEASHING THE POTENTIAL OF NATURAL PRODUCTS LIBRARIES BY SYNTHETICALLY CONSTRAINED AI-DRIVEN ENUMERATION

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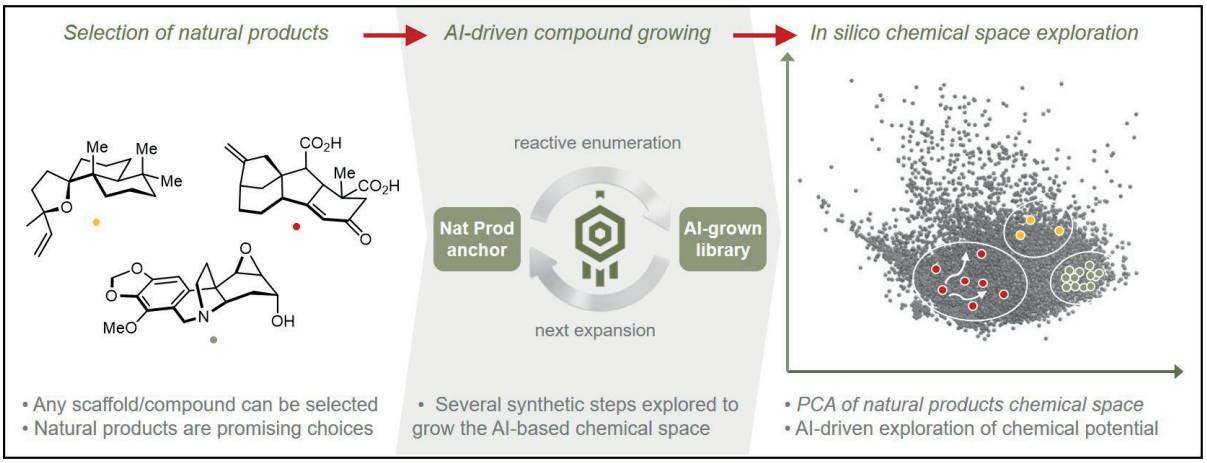


Natural products (NPs) are well known for being a valued source of biologically active molecules.[1] However, when spotted as promising hits, they often prove to be highly difficult to optimize by medicinal chemists. Indeed, natural substances may be sensitive to reaction conditions, too bulky or simply not versatile enough to enable sufficient derivatization and chemical space exploration for designing a robust drug candidate. That hurdle prevents their use in most medicinal chemistry projects and therefore represents a critical scientific challenge. The present work proposes to address this challenge by leveraging a purely data-driven approach of organic synthesis.

Recent papers have reported successful implementation of data-driven AI approaches to retrosynthetic analysis.[2] We extracted chemical reactions and synthetic rules from the USPTO database, as described by Segler *et al.,* in their seminal work on retrosynthesis.[3] We curated and selected several hundreds of natural compounds from the ChEBI database.[4] Then, applying data-driven retrosynthetic rules in the forward direction, we generated a library of synthetically accessible NP-derived molecules. Those compounds are intrinsically designed to be druggable, and accessible *via* a limited number of synthetic steps, from the NP starting point and commercially available starting materials. Moreover, our method provides means to assess the synthetic potential of NPs and to generate the accessible chemical space for a chosen scaffold.

To our knowledge, such data-driven *in silico* synthetic approach is unprecedented. Moreover, its application to overcome the synthetic challenge of NP-related compounds reported in this work is of particular interest for the medicinal chemists community. Not only does our work allow to perform virtual screening of a large library of readily accessible NP-derived compounds, it also empowers medicinal chemists with a sense of the chemical potential of a natural series, by *in silico* synthetic mapping.

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# FRAGMENT-BASED IDENTIFICATION OF SPIRE/FMN2 INHIBITORS

**Radoslaw Kitel, Ewa Surmiak, Przemyslaw Golik, Miroslawa Czub, Tad A. Holak**

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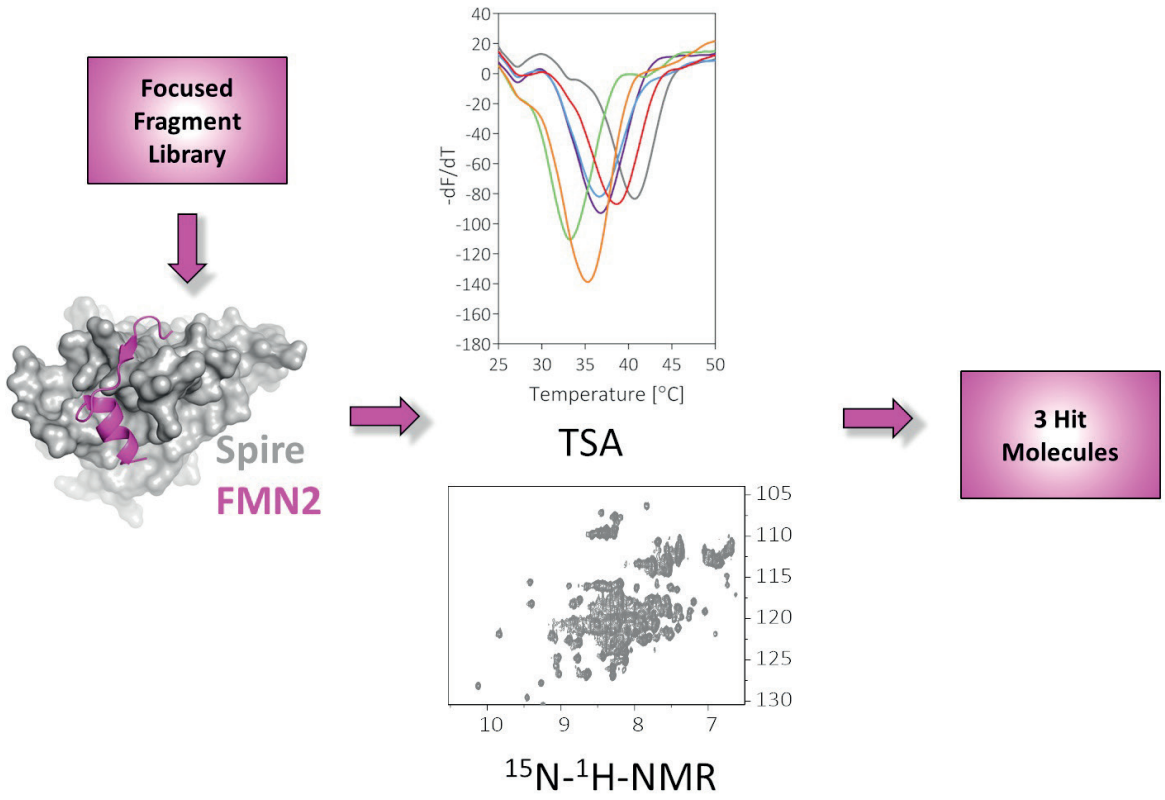
Actin nucleators together with other actin-binding proteins govern and control actin assemblies in cells. Many actin nucleators like Arp2/3 complex, formins and Spire have been reported to play important roles in the development of metastasis what makes them attractive as therapeutic targets. Currently only pharmacological modulators of Arp2/3 complex and formins are available. To fill this gap in the chemical toolbox of actin nucleators inhibitors, we pursued identification of first-in-class compounds targeting Spire1/FMN2 interface.

Given the structural knowledge of the Spire1/FMN2 interface, a focused chemical library of fragments was assembled by selecting compounds from our in-house collection. The final library of fragments contains 120 molecules and was screened against Spire1 using thermal shift assay (TSA). The assessments from the first line screening were then evaluated using $^{15}N$-$^{1}H$ NMR spectroscopy using uniformly labeled $^{15}N$-Spire. Collectively, our approach led us to identification of three fragment-like molecules which will serve as starting points for development of more potent inhibitors.

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# NOVEL ATYPICAL 5-HT6 RECEPTOR ANTAGONISTS

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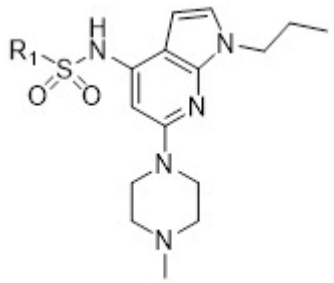
The expression of 5-HT6 receptor is limited to the central nervous system (CNS). This receptor is mainly present in brain regions that mediate cognition, memory and emotions. 5-HT6 receptor antagonism is suspected to modulate the balance between glutamate and GABA, and this approach may be used for the symptomatic treatment of Alzheimer's disease.

5-HT6 is a G-protein coupled receptor, positively coupled to adenylate cyclase. Its stimulation results in an increase in cyclic adenosine monophosphate (cAMP) release, and its intracellular concentration can be used to classify ligands based on their agonist/antagonist activities.

Our studies on 5-HT6 receptor lead to the new type of bis-aryl sulfonamides antagonists with good potency and selectivity. New synthesized structures were based on 1H-pyrrolo[2,3-b]pyridine core substituted in position 4 with different aryl sulfonamides:




SAR analysis of synthesized compounds resulted in the best modification in the aromatic system R1 of the sulfonamide moiety with nanomolar activity on 5-HT6 receptor. Further development with the best modification in R1 considered different aliphatic modifications and also substitution of piperazine moiety with analogues. All studied compounds were docked in homology models of 5-HT6 and D2 receptors to understand the molecular interactions that could influence affinity and selectivity towards 5-HT6R.

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