DRUG DISCOVERY Conference 2026

3rd DRUG DISCOVERY CONFERENCE,
Riga, September 24–25, 2026

Abstract Book

The conference is organized by
National Institute of Research and Innovation & EU-OPENSCREEN

The conference organizers gratefully thank the benefactors:

The conference is organized by the National Institute of Research and Innovation and financially supported by the European Regional Development Fund "Support for international cooperation projects in research and innovation in Latvian Institute of Organic Synthesis" (contract No. 1.1.1.5/18/I/007)

Developing therapeutic vaccines: from basic research to clinical application

Martin F. Bachmann

University of Bern
Department of Immunology, University Clinic for Rheumatology and Immunology, Inselhospital, Bern, Switzerland;
Nuffield Department of Medicine, The Jenner Institute, University of Oxford, Oxford, UK

Monoclonal antibodies (mAbs) have revolutionized medicine due to unprecedent specificity and efficacy, in particular for the treatment of chronic diseases. Despite this undeniable success, mAbs still have several shortcomings, including frequent dosing, potential of inducing anti-drug antibodies and in particular high costs of good. The latter severely restricts access of less affluent individuals and societies to these revolutionary biologics. Replacing passive immunization using mAbs by active immunization with therapeutic vaccines is an attractive concept, as it would solve all of the above-mentioned issues. However, despite some successes, the field remains sceptic vis-à-vis this active vaccination proposition. We have recently developed a number of such therapeutic vaccines in companion animals and demonstrated induction of efficacious and long-lived antibody responses using virus-like particle (VLPs)-based vaccines. Application ranged from allergy to chronic itch and chronic pain. The dossier of a vaccine targeting IL-5 in horses has been submitted for registration. We believe that these therapeutic vaccines in companion animals not only represent significant value as they stand but also pave the way for the development of corresponding vaccines in humans.

Discovery of a non-canonical GRK2-dependent β₂-adrenergic receptor pathway linking receptor signaling to skeletal muscle metabolism

Tore Bengtsson

Stockholm University

Skeletal muscle is central to glucose homeostasis and represents an attractive therapeutic target in metabolic disease. Classical β₂-adrenergic receptor (β₂AR) agonists can stimulate glucose uptake and anabolic responses in muscle, but their clinical utility is limited by cardiovascular effects, receptor desensitization and canonical Gs/cAMP signaling.

We identified a non-canonical β₂AR pathway in which GRK2 acts as a signaling scaffold linking receptor activation to mTORC2-dependent GLUT4 translocation and insulin-independent glucose uptake. Based on this biology, ATR-258 was developed in collaboration with the Latvian Institute of Organic Synthesis (LIOS) as an orally available GRK2-biased β₂AR modulator designed to preferentially engage metabolic and anabolic signaling while limiting classical β-adrenergic effects.

ATR-258 and related pathway-selective compounds stimulate glucose uptake and muscle-associated anabolic signaling with limited β-arrestin recruitment and sustained receptor responsiveness. In preclinical models, GRK-biased β₂AR activation improves glucose metabolism and body composition, reducing fat mass while preserving or increasing lean mass. These effects can complement established metabolic therapies and support a broader role for muscle-directed β₂AR modulation in obesity and related disorders.

ATR-258 has progressed into clinical development, where initial studies have provided human safety, tolerability and pharmacodynamic support for further evaluation. Additional human studies specifically addressing skeletal muscle and body composition are ongoing and are expected to further establish the potential of GRK-biased β₂AR signaling as a therapeutic strategy for improving metabolic health and body composition, especially the muscle.

Assault, siege, Trojan horses or gentle disarmament: molecular strategies to fight drug-resistant bacterial infections

Mark Brönstrup

Helmholtz Centre for Infection Research, Braunschweig, Germany;
German Centre of Infection Research, Site Hannover-Braunschweig, Germany;
Leibniz University Hannover, Germany

Multidrug resistant bacterial pathogens have become a major health concern. We have investigated various chemical strategies for selective targeting, breaking resistance or ameliorating bacterial infections. A broad spectrum of gram-positive and gram-negative pathogens is addressed by cystobactamids, oligo-arylamides originally isolated from Cystobacter sp. Our efforts to optimize the antibiotic properties of the cystobactamids by medicinal chemistry to resistance-breaking, in vivo active leads will be presented [1]. Beyond a classic '*assault'* of bacteria with such antibiotics, the conjugation of natural products to targeting functions has been beneficial to improve their drug properties. In the so-called *Trojan Horse* Strategy, antibiotics are conjugated to siderophores to hijack the bacterial iron transport system, and thereby enhance the intracellular accumulation of drugs. We prepared novel artificial siderophores, characterize their transport and resistance mechanisms, and their ability to deliver large cargo for the treatment of infections [2, 3]. First data for infection imaging in humans with the PET-probe Ga-SIGA will be shown. A triggered release of antibiotic conjugates was realized in the alternative *siege* concept, using the lipopeptide colistin as the antibiotic effector [4, 5]. Finally, our research and development program for first-in-class, in vivo active hemolysin-alpha inhibitors that *disarm* the pathogen *S. aureus* will be shown [6].

References

1. Kulike-Koczula, *Nat. Prod. Rep* **2026**, in press. DOI: 10.1039/D5NP00053J
2. Peukert, *Angew. Chem. Int. Ed.* **2022**, e202201423. DOI: 10.1002/anie.202201423
3. Peukert, *Chem. Sci.* **2023**, *14*, 5490–5502. DOI: 10.1039/D2SC06850H
4. Tegge, *Angew. Chem. Int. Ed.* **2021**, *60,* 17989-17997. DOI: 10.1002/anie.202104921.
5. Charoenpattarapreeda, *Angew. Chem. Int. Ed.* **2024**, e202408360. DOI: 10.1002/anie.202408360
6. Shekhar, *Cell Host Microbe* **2025**, *33*, 560–572. DOI: 10.1016/j.chom.2025.03.006.

Targeting lipid metabolism to improve the type 2 diabetic heart

Marcos Castro-Guarda

University of Oxford

Cardiovascular disease is the leading cause of mortality in type 2 diabetes patients, however, the mechanisms linking diabetes to heart failure remain unclear. The heart becomes metabolically abnormal early on in type 2 diabetes, and our research aims to understand how these alterations contribute to cardiac dysfunction and disease progression. We investigate how metabolites act not only as substrates to produce cellular energy, but also as regulators of cellular function, and how changes in metabolite concentrations, driven by metabolic remodelling in the diabetic heart, influence metabolite-sensitive signalling pathways and alter cellular processes. Our work has shown that lipid metabolites that accumulate in the diabetic heart can affect transcription, modulate post-translational modifications, and allosterically regulate enzyme activity, thereby reprogramming cardiomyocyte function. Ultimately, by understanding the processes controlled by these metabolic alterations, we can start to unravel the pathophysiology of the diabetic heart and identify new metabolic targets with potential therapeutic roles.

The synthesis of polypharmacophore organic compounds by tandems of multicomponent reactions

Valentyn Chebanov[1,2], Yana Sakhno[1], Vladyslav Honcharov[1], Tetiana Savluk[1], Maryna Mazur[1], Alexander Tsygankov[1,3]

[1] Institute of Functional Materials Chemistry, SSI "Institute for Single Crystals" NAS of Ukraine, Nauky ave. 60, Kharkiv, 61072, Ukraine; e-mail: chebanov@isc.kh.ua
[2] Education and Research Institute of Chemistry, V. N. Karazin Kharkiv National University, Svobody sq. 4, Kharkiv, 61077, Ukraine
[3] National Technical University "Kharkiv Polytechnic Institute", Kyrpychova st. 2, Kharkiv, 61002, Ukraine

Multicomponent reactions (MCRs) represent some of the most efficient and versatile approaches for solving problems in organic chemistry. Techniques employing MCRs – like using strategy of chemo-controlled reactions and combinations of multicomponent reactions – have demonstrated usefulness.

We used 3CR of 3-amino-5-methylisoxazole, aromatic aldehydes, and α-ketoglutaric acid to obtain pyrrolone derivatives with a free carboxyl group. Peptidomimetics were then produced via Ugi-4CR. If the Ugi products contained an *ortho*-azidoaryl group, aza-Wittig reactions enabled the synthesis of novel quinoxalinone derivatives.

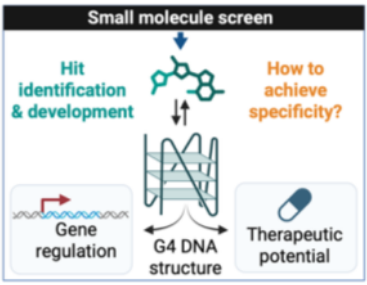
N-(2-amino-1-(2-azidophenyl)-2-oxoethyl)propiolamides were efficiently synthesized via Ugi-4CR using 2-azidobenzaldehyde, amines, isocyanides, and propargyl acids. A further step involving intramolecular azide-alkyne cycloaddition yielded 4-oxo-5,6-dihydro-4H-benzo[f][1,2,3]triazolo[1,5-a][1,4]diazepines. These compounds showed notable anxiolytic and antidepressant effects *in vivo*.

The application of 2-(1-(*tert*-butyl)-1H-tetrazol-5-yl)propan-2-amine, synthesized via the azido-Ugi reaction, in a subsequent Ugi-4CR did not consistently produce conventional Ugi bisamides. When *para*-substituted benzaldehydes, butanal, or pentanal were employed, only atypical post-Ugi transformation products – 3,4-disubstituted morpholine-2,5-diones – were isolated. In contrast, the use of simple aliphatic aldehydes (C1-C3) facilitated the isolation of Ugi bisamides. Comparable results were observed when using 2-(1-cyclohexyl-1H-tetrazol-5-yl)propan-2-amine as the amine component in the Ugi-4CR for all examined aldehydes. Furthermore, it was demonstrated that Ugi bisamides are amenable to post-Ugi transformations yielding morpholine-2,5-diones.

From screening hits to sequence-directed precision: targeting G-quadruplex DNA

Erik Chorell

Department of Chemistry, Umeå University,
Chemical Biology Consortium Sweden (www.cbcs.se), Sweden
erik.chorell@umu.se



G-quadruplex (G4) DNA structures are non-canonical structures implicated in transcription, replication and diseases such as cancer. To identify chemical starting points for their modulation, we developed a thioflavin T displacement assay and screened approximately 28,000 compounds using the compound collections and screening infra-structure of the Chemical Biology Consortium Sweden. Parallel screening against three structurally different G4s enabled selectivity to be considered during hit identification. Eight novel G4 binders were identified, and orthogonal assays confirmed compounds that stabilized G4 DNA and discriminated between different G4 structures.[1]

Medicinal-chemistry development of a quinazoline hit generated more potent compounds that stabilized G4s in cells, perturbed DNA replication and activated DNA-damage responses.[2] Subsequent studies using focused compound series and comple-mentary FRET melting, binding, polymerase-stop and NMR assays identified potent ligands with nanomolar affinities and strong selectivity for G4 over duplex DNA.[3,4] These studies demonstrated how relatively small structural changes can strongly influence G4 binding, stabilization and cellular activity.

However, reliable recognition of one chosen genomic G4 remains difficult because G4s share a conserved ligand-binding surface. We therefore developed G4-ligand-conjugated oligonucleotides, or GL-Os, in which a G4-binding ligand is linked to an oligonucleotide complementary to the sequence flanking the target G4.[5,6] Combined recognition of structure and sequence enables selective binding and stabilization while limiting off-target interactions.

This progression from screening hits to sequence-guided targeting illustrates how open screening infrastructures can generate both bioactive compounds and new approaches to drug discovery.

References

1. Jamroskovic, J.; Livendahl, M.; Eriksson, J.; et al. *Chem. Eur. J.* **2016**, *22*(52), 18932.
2. Jamroskovic, J.; Doimo, M.; Chand, K.; et al. *J. Am. Chem. Soc.* **2020**, *142*, 2876.
3. Andreasson, M.; Donzel, M.; Abrahamsson, A.; et al. *J. Med. Chem.* **2024**, *67*(3), 2202.
4. Bhuma, N.; Chand, K.; Andréasson, M.; et al. *Eur. J. Med. Chem.* **2023**, *248*, 115103.
5. Abrahamsson, A.; Berner, A.; Golebiewska-Pikula, J.; et al. *Bioconjugate Chem.* **2025**.
6. Berner, A.; Das, R. N.; Bhuma, N.; et al. *J. Am. Chem. Soc.* **2024**, *146*(10), 6926.

Protein degraders as chemical tools and drugs

Alessio Ciulli FRS FRSE FRSC

Professor of Chemical Structural Biology
Founder and Director, Centre for Targeted Protein Degradation
Faculty of Life Sciences, University of Dundee, Dundee, United Kingdom

Our laboratory at the Centre for Targeted Protein Degradation (CeTPD) reveals molecular information on protein interactions and ubiquitination complexes and mechanisms to design novel therapeutic concepts. Protein degraders, also known as PROTACs (PROteolysis-TArgeting Chimeras) and molecular glues, recruit a target protein to a ubiquitin E3 ligase for targeted protein degradation. Formation of a stable ternary complex between the degrader, the E3 ligase and the target is a critical step that leads to productive tagging of the target protein by ubiquitination, and subsequent proteasomal degradation. Our research has illuminated fundamental structural and biophysical insights into molecular recognition and mechanism of action of protein degraders, that have guided the design and optimization of novel small molecules for hard-to-target proteins. I will be reflecting on the evolution of the TPD field, from early design principles to today's landscape of PROTACs and molecular glues. Latest advances from the Lab in mechanistic understanding and chemical structural biology of degraders ternary complexes will be showcased. I will also highlight collaborative academic-industry consortia tackling grand challenges with undruggable targets in pediatric cancers and neurodegenerative diseases, charting the next-generation of proximity-based therapeutics.

Developing initial hits towards candidates in TB drug discovery

Laura Cleghorn

University of Dundee

The transition from initial “hits” to validated drug candidates in tuberculosis (TB) drug discovery, requires the integration of diverse expertise, resources, and technologies. This talk will explore how collaborative approaches can accelerate and strengthen the TB drug discovery pipeline. Focusing on the journey from early screening hits to optimised lead candidates, the presentation will highlight use case studies to highlight how multidisciplinary collaboration enhances target validation, structure–activity relationship (SAR) development, and early assessment of pharmacokinetics and efficacy. Ultimately, this work underscores that advancing TB drug discovery is not solely a scientific challenge but a collaborative endeavour – where integrated partnerships are essential to transform promising hits into viable therapeutic candidates capable of addressing a persistent global health burden.

Designing drug discovery for a 'build-to-buy' strategy

Scott L. Dax MS PhD

DRx Pharma Consulting & Services LLC

Pharmaceutical companies de-risk their portfolio by obtaining external assets, investing in platforms & programs belonging to small biotechs, and in some cases, by acquiring private biotechnology companies. Most large pharma houses have dedicated internal 'venture' and 'innovation' groups to search and evaluate external opportunities to diversify, complement and strengthen the parent pipeline.

In order to position a biotech for success as measured by investment, partnership or acquisition, it is necessary to structure and implement Drug Discovery operations to anticipate the demands of large pharma. In response, conducting a "*research to drive business*" mantra is needed which can often be in contrast and even opposition to the core biotech 'pride & personality', and that of a "*business that does research."* Entrepreneurs need to first decide the acceptable fates of their company. While this seems straightforward, it is common to default to doing *research at all costs* without planning for an exit or an end. Secondly a business-centric approach to guide research activities and milestones is needed to optimize the chances for success. This includes repeating and expanding experiments that previously gave exciting results, validating procedures and subjecting data to external Quality Control (QC), conducting early 'killer' experiments and following regulatory guidelines and requirements, however mundane to the entrepreneurial scientist. Lastly, there needs to be an ongoing dialog with any potential partner / investor / acquirer, unburdened by adversity, and with common goals.

CerSci Therapeutics, acquired by Acadia Pharmaceuticals for >$50M USD with a potential $940M total deal, will be used to illustrate *designing Drug Discovery for a 'Build-to-Buy' Strategy*.

Synthetic cannabinoid receptor agonists as a case study in CNS drug characterization: behavioural and neurochemical evidence

Maria Antonietta De Luca, PhD

Department of Biomedical Sciences, University of Cagliari (Italy)
deluca@unica.it

Synthetic cannabinoid receptor agonists (SCRAs) represent the largest class of novel psychoactive substances worldwide, with use rising particularly among adolescents via e-cigarette vaping (EMCDDA, 2026). As highly potent full agonists of cannabinoid receptors, SCRAs induce more severe withdrawal symptoms and cognitive impairments compared to THC, thereby elevating risks for cannabis use disorder and psychiatric risks following protracted use; yet the neurodevelopmental consequences of adolescent exposure remain poorly characterized.

Here we present a behavioural and neurochemical characterization of two SCRAs, the prototypical compound JWH-018 and the newer and more potent 5F-MDMB-PICA, across passive, adolescent, and adult exposure paradigms, as a case study in translational CNS drug assessment. We evaluated the enduring effects of repeated JWH-018 exposure via passive administration in adult (0.25 mg/kg i.p. for 14 days) and adolescent (0.3 mg/ml vapor for 21 days) rats. In adult male rats, repeated JWH-018 exposure induced anxious/aversive behaviour, decreased spontaneous activity and dopamine (DA) neuron number in the VTA, and changes mPFC and NAc shell DA responsiveness to salient stimuli (i.e., chocolate taste) accompanied by astrogliosis (mPFC, NAc shell/core, VTA), microgliosis (NAc shell/core), and CB1 receptor downregulation (mPFC, NAc shell/core) (Pintori et al., 2021 doi.org/10.1111/bph.15494). In adolescent male and female rats, we further characterized the pharmacokinetic profile of JWH-018 in plasma following vapor inhalation and identified a sex-specific loss of mPFC and/or NAc shell DA responsiveness to chocolate taste as estimated by in vivo brain microdialysis (Pintori et al., 2026 doi.org/10.1111/bph.70223). In a second model, adult male mice with an adolescent 5F-MDMB-PICA self-administration history (2.5 µg/kg/25µl/infusion) exhibited a stress-vulnerable phenotype (i.e., increased aggression, reduced social interaction, and anhedonia) accompanied by a blunted, delayed mPFC DA response and reduced calcium transients in mPFC excitatory neurons to an olfactory stressor (i.e., predator odor) (Caria et al., 2025 doi.org/10.1101/2025.06.26.661592). Together, these *in vivo* rodent models demonstrate that structurally distinct SCRAs produce lasting, sex- and paradigm-dependent disruption of mesocorticolimbic circuits governing reward, cognition, stress reactivity, and neuroimmune function. These findings support integrated behavioural-neurochemical-immune profiling as a necessary framework for characterizing the emerging CNS drugs.

Nature-inspired peptide libraries for GPCR drug discovery

Christian W. Gruber

Center for Physiology and Pharmacology, Medical University of Vienna, Austria

Peptides are central mediators of intercellular communication and exert many of their biological effects through G protein-coupled receptors (GPCRs), the largest and most pharmacologically tractable receptor family. Despite their high potency and selectivity, the therapeutic development of peptide ligands has been limited by poor metabolic stability and an incomplete understanding of receptor-specific signalling mechanisms. In this seminar, I will present peptide-based strategies for GPCR drug discovery that integrate natural peptide mining, pharmacology-guided screening, as well as rational and computational design, while also leveraging peptides as molecular tools to dissect GPCR signalling. By exploiting diverse natural scaffolds, we generate peptide ligands with enhanced stability, improved receptor selectivity, and finely tuned signalling profiles. Selected examples targeting the κ-opioid receptor, oxytocin/vasopressin receptors, and the cannabinoid 2 receptor illustrate how stabilized peptides enable detailed exploration of molecular signalling properties and how functional specificity and improved drug-like characteristics can be achieved, highlighting the potential of peptides as next-generation therapeutic candidates.

A chalcogen impact on the multitarget action of 1,3,5-triazine 5-HT_6 receptor agents in search for new therapies of Alzheimer's disease

Jadwiga Handzlik

Chair of Chemical Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland
j.handzlik@uj.edu.pl

Alzheimer's disease (AD) is a serious civilization problem and high challenge of current medicine due to highly complex etiology. The current AD pharmacotherapy improves memory and cognitive functions of patients but cannot inhibit progressive neurodegeneration. With respect to the complex etiology, including the cellular hallmarks, nine AD hypotheses have been proposed to be useful key points in search for new successful therapies [1]. In this context, an exceptional brain location of 5-HT_6 serotonin receptor (5-HT_6R) and increasing knowledge about its functional activity give wide perspectives for an application of 5-HT_6R agents in development of a new therapy referring to several of AD hypotheses. However, these promising prospects have not yet translated into any success in pharmaceutical market, as none, out of seventeen 5-HT_6R antagonists in clinical trials, has passed Phase III. Among main reasons of this clinical failure, a too narrow structural variety, limited predominantly to sulfone- or indole - containing structures of 5-HT_6R agents, is mentioned. Thus, searching for multitargeting 5-HT_6R agents in extended, beyond the indole- and sulfone-containing, chemical space has been highly desired. In response to this challenge, we proposed an original non-indole and non-sulfone group of 1,2,3-triazine derivatives that, within the subsequent pharmacomodulation including an introduction of various chalcogens into linkers, has evolved from selective 5-HT_6R- to multitargeting pharmacological profile translated into memory-protective properties in animal models. Thus, the chalcogen role for either 5-HT_6R intrinsic activity or extended pharmacological profile, in the context of therapeutic possibility in AD treatment [2], for the series of 1,3,5-triazines, has been analyzed and discussed within this study.

Acknowledgements
This research was partly funded by the National Science Centre, Poland (grant UMO-2023/51/B/NZ7/02177).

References
1. Karran, E., De Strooper, B. *Nat. Rev. Drug Discovery* **2022**, *21*, 306;
2. Pyka, P. et al. *J. Med. Ch*em. **2024**, *67*, 1580.

BRICHOS domain crosses brain vascular endothelial cells and inhibits Ab toxicity in Alzheimer's disease models

Jan Johansson

Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

The idea that BRICHOS functions as an endogenous defense against amyloid toxicity emerged from studies of lung surfactant protein C (SP-C), a protein with an exceptionally high amyloid-forming propensity. In its precursor, SP-C is protected from amyloid aggregation by a BRICHOS domain, which interacts also with proteins implicated in amyloid diseases, including Aβ42 associated with Alzheimer's disease (AD).

Recombinant human (rh) BRICHOS derived from the Bri2 protein crosses the blood–brain barrier (BBB) in mice. In AD mouse models, App^{NLF} and App^{NLGF}, repeated intravenous injection of rh Bri2 BRICHOS over three months was well tolerated and resulted in significant improvements in spatial and working memory. Treatment was further associated with attenuation of reactive astro- and microgliosis, a particularly interesting feature as neuroinflammation is recognized as a critical driver of AD progression.

BRICHOS potently suppresses Aβ42-induced neurotoxicity by selectively inhibiting secondary nucleation on the surface of existing amyloid fibrils. This mechanism distinguishes BRICHOS from currently developed anti-Aβ monoclonal antibodies, which are comparatively inefficient at inhibiting secondary nucleation. Transcytosis of rh Bri2 BRICHOS across human cerebral microvascular endothelial cells is saturable, bidirectional and requires active dynamin. Proximity labelling suggest that rh Bri2 BRICHOS interacts with multiple cell-surface proteins with moderate affinity, resembling its established promiscous binding to b-sheet fibrils. Moreover, brain homogenates from App^{NLGF} mice contain soluble membranolytic Aβ oligomers, while in brains from App^{NLGF} mice that have been treated with rh Bri2 BRICHOS the amounts of such Aβ oligomers are markedly reduced. Rh Bri2 BRICHOS also suppresses Aβ oligomer–induced damage in human cortical neurons and reduces the secretion of pro-inflammatory cytokines by human astrocytes. Finally, spatial transcriptomics of App^{NLGF} mouse brains show that rh Bri2 BRICHOS treatment attenuates the expression of AD plaque-induced genes and immunomodulatory genes.

Synthesis of visible light photoswitchable peptides

Xavier Just-Baringo

Laboratori de Química Orgànica, Facultat de Farmàcia,
Universitat de Barcelona, 08028 Barcelona, Spain
xavier.just@ub.edu

Photopharmacology enables the use of light to control the activity of drugs with temporal and spatial precision.[1] Among the available scaffolds to incorporate this property into biologically active molecules, azobenzenes outshine most alternatives due to their versatility and ample room for tweaking their properties. Functionalisation of azobenzene photoswitches has enabled the use of visible light as a means to achieve such control. Although many kinds of drugs have been modified with photoswitchable moieties, antibiotics are among those more urgently needing a revolution in their development.[2,3] Also, antimicrobial peptides are getting more attention as drug candidates. The combination of visible light operated azobenzenes and peptides has been hugely hampered by the available building blocks and the limitations of the existing synthetic methods.[4,5] We have developed mild and general conditions for the synthesis of tetra-*ortho*-methoxylated azobenzenes, including amino acid analogues that are fully compatible with Solid Phase Peptide Synthesis.[5]

References

1. Hüll, K.; Morstein, J.; Trauner, D. *Chem. Rev.* **2018**, *118*, 10710.
2. Just-Baringo, X.; Yeste-Vázquez, A.; Moreno-Morales, J.; Ballesté-Delpierre, C.; Vila, J.; Giralt, E. *Chem. Eur, J.* **2021**, *27*, 12987.
3. (a) Konrad, D.B.; Frank, J.A.; Trauner, D. *Chem. Eur. J.* **2016**, *22*, 4364. (b) Liu, Q.; Luo, X.; Wei, S.; Wang, Y.; Zhu, J.; Liu, Y.; Quan, F.; Zhang, M.; Xia, C. *Tetrahedron Lett.* **2019**, *60*, 1715.
4. (a) Hansen, M. J.; Lerch, M. M.; Szymanski, W.; B. L. Feringa, B. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 13514. (b) Müller-Deku, A.; Thorn-Seshold, O. *J. Org. Chem.* **2022**, *87*, 16526.
5. Ruiz-Soriano, A.; Lamelza, L.; Pizzamiglio, E.; Just-Baringo, X. *J. Org. Chem.* **2024**, *89*, 17141.

Mastering drug targets with light using photosensitive molecules

Rob Leurs

Department of Medicinal Chemistry, Vrije Universiteit,
Amsterdam the Netherlands
r.leurs@vu.nl

Temporal and spatial control of protein function can be obtained by the use of a new class of so-called photoswitchable ligands. Photoswitchable ligands can reversibly photoisomerize from the *trans* to *cis* isomer upon illumination with specific wavelengths. Such a light-induced conformational change in the ligand may result in temporal and spatial changes in pharmacological profile.

In view of the potential of this new field of photopharmacology, we have recently analyzed the currently available photoswitches for family A GPCRs [1]. Moreover, we will show several in-house developed examples for the optical control of GPCR function, incl. histamine receptors and the $beta_2$ adrenoceptor. For these receptors, we have set out to develop small-molecule ligands with photoswitchable affinity (H_3 and H_4 receptor, the $beta_2$ receptor) or efficacy in which both configurations bind the target protein but exert distinct pharmacological effects ($beta_2$ receptor), that is, stimulate or antagonize GPCR activation.

We will show how these ligands allow optical control of GPCR function in a variety of *in vitro* and *in vivo* models and are novel valuable pharmacological tools to study protein function in cell signaling.

References

1. Maikel Wijtmans, Ivana Josimovic, Henry F. Vischer and Rob Leurs. Optical control of Class A G protein-coupled receptors with photoswitchable ligands. Current Opinion in Pharmacology, 63, 102192 (2022).

Thioquercetins as novel anticancer and senotherapeutic agents: potentiated effects against melanoma cells upon HSP90 inhibition

Anna Lewinska

Faculty of Biotechnology, Collegium Medicum,
University of Rzeszow, Pigonia 1, 35-310, Rzeszow, Poland
e-mail: alewinska@ur.edu.pl

Drug-induced senescence, a side effect of chemotherapy, may limit the elimination of cancer cells, especially senescent cancer cells. Thus, there are attempts to design and test compounds and nanodevices that are active against senescent cells, namely senolytics and nanosenolytics, respectively. One class of reported senolytics are natural compounds such as flavonoids, e.g., quercetin and fisetin, but their senotherapeutic applications require further improvements. In the framework of NANO4ZOMBIE project, we have focused on the screening of novel quercetin derivatives (QDs) with improved anti-melanoma and anti -senescence activity. We have analyzed fourteen QDs (e.g., methoxy, aza, acetyl, and thiocarbonyl quercetins) in several 2D and 3D cellular models of melanoma *in vitro*. Three thioquercetins: thioQ (without modified hydroxy groups), thioQ$(OAc)_4$ (with four acetylated hydroxy groups), and thioQ$(OAc)_5$ (with five acetylated hydroxy groups) promoted more pronounced cytotoxic and/or antiproliferative effects than parent compound quercetin. In selected experimental settings, thioQ$(OAc)_4$ was also active against drug resistant senescent melanoma cells. HSP90 inhibition by using pharmacological inhibitor 17-DMAG potentiated antimelanoma activity of thioquercetins as judged by oxidative stress-mediated apoptosis and affected AhR/CYP1A1 detoxification pathway. We suggest that thioquercetin treatment and HSP90 inhibition may be considered as a new antimelanoma strategy upon further validation *in vivo*. Moreover, we selected thioQ$(OAc)_4$ as one of components of a novel multifunctional nanoplatform (iron oxide nanoparticles plus anti-senescent melanoma specific antibody plus senolytic drug) to be tested against drug-induced senescent melanoma cells as a future research plan.

Acknowledgements
This study was conducted in the framework of M-ERA.NET 3 Call 2022 and supported by the National Science Centre (NCN, Poland) grant No. 2022/04/Y/ST5/00155, Latvian Council of Science grant No. ES RTD/2023/38, and MICIU/AEI/10.13039/501100011033 grant No. PCI2023-143448, and co-funded by the European Union.

References
Apoptosis (2026) 31:114; https://doi.org/10.1007/s10495-026-02311-4

The effects of thioquercetin on the senescence-associated secretory phenotype of melanoma cells

Aleksandrs Dumešs[1], Edgars Endzeliņš[1], Lilite Sadovska[1], Nadezhda Romanchikova[1], Wojciech Witkowski[2], Grzegorz Litwinienko[2], Aija Linē[1]

[1] National Institute of Research and Innovation, Riga, Latvia
[2] Faculty of Chemistry, University of Warsaw, Warsaw, Poland
e-mail: aija.line@niri.lv

Senescent cancer cells primarily influence the tissue microenvironment through the senescence-associated secretory phenotype (SASP) – a potent cocktail of pro-inflammatory cytokines, growth factors, chemokines, and matrix metalloproteinases that can exert both tumor-promoting and anti-tumor effects. These signaling molecules are secreted either in soluble form or encapsulated within extracellular vesicles (EVs). Within the framework of the NANO4ZOMBIE project, we investigated the effects of total and EV-associated melanoma SASP on primary cells within the tumor microenvironment, and evaluated the capacity of a novel thioquercetin derivative to modulate this activity.

Therapy-induced senescent melanoma cells were generated by treating the A375 cell line with 4 μM cisplatin. EVs were subsequently isolated from untreated A375 cells, senescent A375 cells, and senescent A375 cells treated with thioQ$(OAc)_5$ – a thioquercetin derivative with five acetylated hydroxy groups that showed a potent antimelanoma activity in a previous study[1]. Untreated A375, senescent A375 and thioquercetin-treated senescent A375 cells or their EVs were co-cultured with patient-derived primary melanocyte and fibroblast cell cultures and the effects on RNA and protein expression were analyzed at a single cell level using Teton CytoProfiling Immunopanel on AVITI24 platform. Comparative analysis between untreated and senescent A375 cells confirmed a senescent phenotype, characterized by the upregulation of BCL2, FAS, IL7R, and CXCR4, alongside the downregulation of the cell cycle regulator CDC28. Notably, treatment of these senescent cells with thioQ$(OAc)_5$ attenuated BCL2 upregulation and induced TP53 expression. Furthermore, co-culturing primary microenvironmental cells with senescent A375 cells or their EVs stimulated the expression of integrins, growth factors, cytokines, chemokines, and their corresponding receptors; however, thioQ$(OAc)_5$ treatment substantially altered and mitigated this cellular response. Taken together, these results provide novel insights into the functional significance of the SASP in melanoma and suggest that thioQ$(OAc)_5$ acts, at least in part, as a promising senomorphic drug.

Acknowledgements
This study was conducted in the framework of M-ERA.NET 3 Call 2022 and supported by the National Science Centre (NCN, Poland) grant No. 2022/04/Y/ST5/00155, Latvian Council of Science grant No. ES RTD/2023/38, and MICIU/AEI/10.13039/501100011033 grant No. PCI2023-143448, and co-funded by the European Union.

References
1. Witkowski W. et al. Apoptosis. 2026;31:114; https://doi.org/10.1007/s10495-026-02311-4

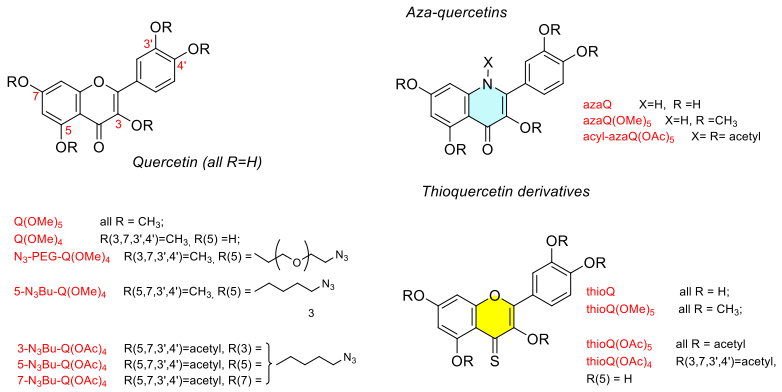
Synthesis and structural optimization of quercetin and thioquercetin derivatives: overcoming the limitations of natural flavonoids

Wojciech Witkowski, Piotr Piotrowski, Michał Żebrowski, Martyna Cybularczyk-Cecotka, Grzegorz Litwinienko

Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland
e-mail: litwin@chem.uw.edu.pl

Despite the vast landscape of modern oncology, there remains a critical need for therapeutic agents that combine high efficacy with minimal systemic toxicity. Quercetin, a naturally occurring polyphenolic flavonoid, has gained significant attention for its multi-targeted anticancer properties, including the modulation of signaling pathways involved in apoptosis, cell cycle arrest, and angiogenesis. To address the pharmacokinetic limitations of quercetin – specifically its low solubility and rapid metabolism – we synthesized fourteen novel quercetin derivatives (QDs) focusing on regioselective modifications of hydroxy groups at the C-3 and C-7 positions. This chemical strategy, including the development of potent thioquercetin analogs, was designed to enhance lipophilicity and metabolic stability while preserving the flavonoid's core pharmacophore. While this presentation focuses on the rational design and structural characterization of these QDs, an accompanying presentation will detail their biological efficacy, including potent senolytic activity and synergistic pro-apoptotic effects in melanoma models when combined with HSP90 inhibitors.

Scheme 1. Methoxy-, aza-, acetyl-, and thiocarbonyl derivatives of quercetin



Acknowledgements
This study was conducted in the framework of M-ERA.NET 3 Call 2022 and supported by the National Science Centre (NCN, Poland) grant No. 2022/04/Y/ST5/00155, Latvian Council of Science grant No. ES RTD/2023/38, and MICIU/AEI/10.13039/501100011033 grant No. PCI2023-143448, and co-funded by the European Union.

References
Apoptosis (2026) 31:114; https://doi.org/10.1007/s10495-026-02311-4

Protein kinases inhibitors: from cancer treatment to neurodegenerative diseases

Ana Martinez[1,2]

[1] Centro de Investigaciones Biológicas "Margarita Salas"-CSIC,
Ramiro de Maeztu 9, 28040 Madrid, Spain
[2] Centro de investigación Biomédica en Red en enfermedades neurodegenerativas (CIBERNED),
Insituto de Salud Carlos III, Spain
ana.martinez@csic.es

Protein kinases are key regulators of cellular signaling, controlling processes such as proliferation, differentiation, survival, metabolism, and inflammation. Dysregulated kinase activity is a hallmark of many cancers and has led to the development of kinase inhibitors that have transformed cancer therapy. Increasing evidence also implicates aberrant kinase signaling in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease. Kinases contribute to pathological processes such as protein aggregation, neuro-inflammation, oxidative stress, impaired autophagy, and neuronal death, making them attractive therapeutic targets. Thus, repurposing or developing kinase inhibitors originally designed for cancer represents a promising strategy for neurodegenerative disorders, with the potential to target disease mechanisms. However, challenges such as blood–brain barrier penetration, target selectivity, long-term safety, and the physiological roles of kinases in the nervous system must be addressed to achieve clinical translation.

The serine/threonine kinases GSK-3 and CK1 exemplify therapeutic targets relevant to both cancer and neurodegeneration. The first ATP non-competitive GSK-3 inhibitor was discovered in our laboratory, leading to the development of tideglusib, which has advanced to clinical trials and demonstrated a favorable safety profile. More recently, CK1 inhibitors capable of reducing TDP-43 phosphorylation have been developed for ALS and have progressed to clinical trials. These compounds may also have potential applications in other TDP-43 proteinopathies and certain cancers. Both experiences from our group will be presented, highlighting the translational journey from target discovery and drug development to clinical trials.

References

1. Baldi, S., Long, N., Ma, S., et al. *Research (Wash D C).* **2025**, *8*, 0747.
2. Lovestone, S., Boada, M., Dubois, B., et al. *J Alzheimers Dis.* **2015**, *45*, 75-88.
3. Cuevas, E.P., Martinez-Gonzalez, L., Gordillo, C., et al. *Neurobiol Dis*. **2024**, *192*, 106430.

Drug discovery programs in Alzheimer's disease – learning through examples sigma-1 receptor agonists, Neuro-EPO and fluoroethylnormemantine

Tangui Maurice

MMDN, University of Montpellier, EPHE, INSERM, Montpellier, France

Addressing an effective therapy, that could be curative, neuroprotective or symptomatic, in complex neurodegenerative diseases such as Alzheimer's diesase (AD) remains terribly challenging. Recent clinical progresses, beyond cholinesterases inhibitors such as Donepezil or the NMDA receptor antagonist Memantine, were allowed thanks to potent anti-Amyloid-ß peptide antibodies or to symptomatic treatments, addressing AD-related agitation for instance. Current pre-clinical strategies are mainly based on drug combinations or multi-target derived ligands that aim to activate simultaneously additive or synergistic neuroprotective targets.

In the MMDN laboratory, we were involved, these last twenty years, in several drug discovery programs that reached the clinical stage. To boost preclinical programs, we used pharmacological and genetic AD models in rodents and we developed either the promising drugs of collaborating groups, or we identified new drugs from large medicinal drug phenotyping screening.

First, we showed the efficacy of Fluoroethylnormemantine, a derivative of Memantine, superior to its parent compound in attenuating neuroinflammation [1, 2]. Second, we demonstrated the efficacy of Neuro-EPO, a low scialic acid form of erythropoietin administrable intra-nasally, in pharmacological and transgenic mouse models of AD [3,4]. Neuro-EPO showed a clear superiority to human recombinant EPO, administered systemically, and a strong effect on cerebral Amyloid-ß load. The formulation (now NeuralCIM) is in clinical use in Cuba since 2022. Third, we discovered the neuroprotective effect of sigma-1 receptor agonists in AD by showing that Donepezil partly act through its sigma-1 receptor agonist activity. We then described the protective effect of ANAVEX2-73 in preclinical models [5, 6]. The compound (now Blarcamesine) underwent successful clinical phases with efficacy in phase 3 and is now discussed with reglementary agencies [7]. More recently, we identified the therapeutic efficacy of sigma-1 receptor agonists in a rare genetic disease, the Wolfram syndrome [8], and from this program, we developed an in vivo phenotypic drug screening in zebrafish. A library of 350 compounds from a medicinal program were screened and among the hits, an optimized lead was characterized.

These programs will be presented and discussed. The associated technological transfer strategies, notably through the involvement of ANAVEX Life Sciences and creation of ReST Therapeutics or SITERA Pharmaceuticals, will be presented.

References

1. Carles A, Freyssin A, Guehairia S, Reguero T, Vignes M, Hirbec H, et al. *Alz Res Ther*. **2025**, *7*, 7.
2. Freyssin A, Carles A, Moha B, Rubinstenn G, Maurice T. *ACS Pharmacol Transl Sci*. **2024**, *7*, 4069.
3. Maurice T, Mustafa MH, Desrumaux C, Keller E, Naert G, de la C. García-Barceló M, et al. *J Psychopharmacol*. **2013**, *27*, 1044.
4. Rodríguez Cruz Y, Strehaiano M, Rodríguez Obaya T, García Rodríguez JC, Maurice T. *J Alz Dis*. **2017**, *55*, 231.
5. Villard V, Espallergues J, Keller E, Vamvakides A, Maurice T. *J Psychopharmacol*. **2011**, *25*, 1101.
6. Lahmy V, Meunier J, Malmström S, Naert G, Givalois L, Kim SH, et al. *Neuropsychopharmacology*. **2013**, *38*, 1706.
7. Macfarlane S, Grimmer T, Teo K, O'Brien TJ, Woodward M, Grunfeld J, et al. *J Prev Alzheimers Dis*. **2025**, *12*, 100016.
8. Crouzier L, Danese A, Yasui Y, Richard EM, Liévens JC, Patergnani S, et al. *Science Transl Med*. **2022**, *14*, eabh3763.

Pridopidine, a potent and selective therapeutic Sigma-1 receptor (S1R) agonist for the treatment of neurodegenerative and neurodevelopmental diseases

May Meltzer[1], Michal Geva[1], and Michael R. Hayden[1,2]

[1] Prilenia Therapeutics B.V., Naarden, The Netherlands
[2] CMMT, University of British Columbia, Vancouver, Canada

Pridopidine, a selective S1R agonist, is being developed for Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and other neurodegenerative and neurodevelopmental disorders. In preclinical models of HD, ALS, Vanishing White Matter (VWM), retinal degeneration, and Rett syndrome, pridopidine restored impaired cellular pathways by preserving mitochondrial-associated membrane (MAM) integrity, improving calcium homeostasis, mitochondrial function, and autophagy, and reducing oxidative and ER stress. S1R activation also enhanced dendritic spine density, synaptic function, and BDNF signaling, supporting neuronal health and survival.

Human PET studies confirmed >90% S1R occupancy at the clinically relevant dose (45 mg bid), and clinical trials have consistently demonstrated a safety profile comparable to placebo. In the Phase 3 PROOF-HD trial (NCT04556656) and its open-label extension, pridopidine improved function, motor symptoms, cognition, and disease progression in HD patients not receiving antidopaminergic medications (ADMs), with benefits sustained over 2 years versus propensity score-matched cohorts from ENROLL-HD and TRACK-HD. These findings are being further evaluated in the pivotal Phase 3 PRECISE-HD trial.

In the Phase 2 HEALEY ALS Platform Trial (NCT04615920), pridopidine slowed disease progression, respiratory decline, and deterioration in bulbar function and speech, while extending median survival in faster-progressing patients. These results supported the ongoing Phase 3 PREVAiLS study (NCT07322003). Pridopidine is also being evaluated in an expanded access program for VWM, where two treated subjects showed stable disease, reduced plasma NfL levels, and increased BDNF, suggesting enhanced neuronal protection.

Overall, pridopidine remains a promising late-stage S1R therapeutic candidate across multiple neurodegenerative diseases.

References

1. Reilmann R, Feigin A, Rosser AE, Kostyk SK, Saft C, Cohen Y, et al. Pridopidine in early-stage manifest Huntington's disease: a phase 3 trial. Nat Med. 2025;31(11):3780–9.
2. Reilmann R, Tan AM, Rosser AE, Chen K, Anderson KE, Kostyk SK, et al. Long-Term Slowing of Progression in Huntington's Disease with Pridopidine Treatment. medRxiv. 2026:2026.02.13.26345490.
3. Geva M, Goldberg YP, Leitner ML, Cruz-Herranz A, Hand R, Chen K, et al. Pridopidine treatment in ALS: subgroup analyses from the HEALEY ALS Platform trial. Amyotroph Lateral Scler Frontotemporal Degener. 2025:1–13.

Rediscovering bacteriophages: from natural antibacterial agents to modern anti-infective medicinal products

Ryszard Międzybrodzki[1,2,3]

[1] Bacteriophage Laboratory, Department of Phage Therapy,
Hirszfeld Institute of Immunology and Experimental Therapy PAS, Wroclaw, Poland
[2] Phage Therapy Unit, Medical Center,
Hirszfeld Institute of Immunology and Experimental Therapy PAS, Wroclaw, Poland
[3] Department of Clinical Immunology, Medical University of Warsaw, Poland

The growing challenge of antimicrobial resistance has renewed interest in bacteriophages as natural antibacterial agents and potential modern anti-infective medicinal products. Although phage therapy has been known for more than a century, its current rediscovery is taking place in a very different scientific, clinical, and regulatory landscape.

This presentation will provide a concise overview of bacteriophages as biologically active and highly specific antibacterial agents. Their unique properties – including targeted activity against bacteria, potential use against drug-resistant infections, interactions with antibiotics, and significant immunomodulatory effects – make them attractive candidates for contemporary anti-infective drug development. At the same time, transitioning from natural biological entities to standardized therapeutics involves navigating complex pharmacokinetic and pharmacodynamic challenges, creating specific hurdles related to phage selection, characterization, manufacturing, quality control, and clinical evaluation.

Consequently, the discussion will outline the broader translational pathway by which bacteriophages may move from natural antibacterial entities and individualized, experimental therapeutic use – informed, among others, by the clinical experience of the Phage Therapy Unit at the Hirszfeld Institute – toward standardized medicinal products. Particular attention will be given to the need for scientific evidence, reproducible methods, defined quality standards, and evolving regulatory frameworks that can accommodate the biological complexity and personalized potential of phage therapy.

Development of a senolytic nanoplatform to target and eliminate skin cancer Zombie cells

María Moros

Instituto de Nanociencia y Materiales de Aragón, Zaragoza, España
mamoros@unizar.es

It is widely accepted that UV, radiotherapy and/or chemotherapy can promote stress-induced premature senescence of normal and/or neoplastic cells. These senescent cells are often called *zombie cells* because they are resistant to cell death and may promote tumour recurrence, metastasis or drug resistance. Therefore, the removal of senescent cancer cells represents a novel and promising anticancer strategy. A number of agents that can selectively kill senescent cancer cells (senolytics) are now identified and tested. However, this solution can be clinically limited as senolytic drugs exhibit relatively low bioavailability and can also promote some side effects.

In the Nano4Zombie project we propose the use of a multifunctional nanoplatform based on magnetic nanoparticles (MNPs) to eliminate skin cancer senescent cells. The MNPs were functionalized with novel therapeutic agents and specific antibodies to selectively carry the drug to *zombie* cells. Besides the site-specific delivery of the drugs, we explored the possibility to produce oxidative stress with the MNPs to reinforce the effect of the drugs. Finally, in the Nano4Zombie project we also evaluated the functional effects of senescent cell-released extracellular vesicles (SCEVs), providing valuable information about their role in skin tumour progression.

Acknowledgements
Nano4Zombie was funded in the M-ERA.NET 3 Call 2022 and supported by the National Science Centre (NCN, Poland) grant No. 2022/04/Y/ST5/00155, Latvian Council of Science grant No. ES RTD/2023/38, and MICIU/AEI/10.13039/501100011033 grant No. PCI2023-143448, and co-funded by the European Union.

Next-generation VLPs as lymphatic nanoplatforms for targeted immune delivery: engaging γδ T cells as a “double-edged” anti-tumor ally

Mona Moshen

University of Bern

Virus-like particles (VLPs) have emerged as versatile nanoscale platforms for delivering therapeutic antigens and immunomodulatory molecules. Their defined architecture, biocompatibility, and repetitive surface geometry enable efficient trafficking to draining lymph nodes after administration, where they interact with immune cell populations that initiate and regulate anti-tumor immunity.

At the University of Bern and DeepVax GmbH, we engineer next-generation VLPs for targeted immune delivery. We have developed modular naked and conjugated VLP platforms that can be adapted to display and deliver diverse therapeutic molecules, and our studies show efficient lymphatic trafficking and uptake by professional antigen-presenting cells, including dendritic cells, macrophages, and

B cells. More recently, we identified efficient VLP uptake by γδ T cells “a double-edged sword”, highlighting these cells as an additional, underexplored target for rapid immune activation in solid tumors.

In this talk, I will focus on how VLP engineering can engage γδ T cells, the field’s “mysterious double agents” to support fast, robust anti-tumor immunity and improve therapeutic efficacy in solid tumor settings.

Tailoring chemical probes for the visualization of the endocannabinoid system

Marc Nazare

Medicinal Chemistry, Leibniz Research Institute for Molecular Pharmacology (FMP), Berlin, Germany
nazare@fmp-berlin.de.

The endocannabinoid system (ECS) is a complex lipid-based signaling network involved in a wide variety of physiological and cognitive processes such as pain regulation, immune response, appetite control, learning and memory formation, cardiovascular regulation, and addictive-like behavior. The ECS has a profound role in pathological conditions such as cancer, immunological disorders, inflammation, neurodegenerative diseases, and drug abuse. However, despite its great therapeutic potential, there are severe hurdles for drugs targeting the ECS, as clinical translatability from preclinical models deduced from different species is currently challenging. Here, labeled chemical probes have propelled advances and breakthroughs in unraveling the underlying biological processes in native cellular environments with unprecedented spatio-temporal resolution, thereby supporting translational efforts.

This talk will focus on the design concepts and development of novel targeting imaging platforms for visualization of main constituents of the endocannabinoid system such as the cannabinoid receptors (CBR) and monoacylglycerol lipase (MAGL). Successful reverse design strategies for the development of a toolbox of potent and efficacious drug-derived selective fluorescent probes and their universal applicability in imaging and mechanism of action studies for characterizing the endocannabinoid system will be discussed.

Highly selective inhibitors of protein kinases with weakly interacting central pharmacophores

Kamil Paruch

Department of Chemistry, Masaryk University, Brno 625 00, Czech Republic
International Clinical Research Center, St. Anne's University Hospital, 602 00 Brno, Czech Republic

Protein kinases regulate numerous cellular signaling pathways in the cell and their aberrant activity may lead to cancer, neurodegenerative, inflammatory, and autoimmune diseases. Targeting this class of enzymes represents one of the most dynamic areas of pharmaceutical research, as evidenced by >80 small-molecule kinase inhibitors approved for clinical use.

Majority of kinase inhibitors are ATP-competitive, with central pharmacophores composed of nitrogen-containing heterocycles that enable interaction with the hinge regions of kinases. The ATP-binding sites across the kinome are highly conserved, which makes identification of highly selective kinase inhibitors a non-trivial task.

We have demonstrated that the weakly interacting furo[3,2-*b*]pyridine core can be used as the basis of highly selective kinase inhibitors of kinases CLK, HIPK, ALK1/2, DDR1 and FLT3. Recently, we have discovered a new series of highly selective inhibitors of the kinase Haspin based on the thieno[3,2-*b*]pyridine scaffold. The weak interaction of the thieno[3,2-*b*]pyridine core with the Haspin hinge region allows the inhibitors to adopt profoundly different binding modes while maintaining high kinome-wide selectivity.

Beyond receptor affinity: biased multimodal signaling of HBK-15 in the search for rapid-acting antidepressant and procognitive strategies

Karolina Pytka[1], Angelika Jagielska[1,2], Kinga Sałaciak[1], Klaudia Lustyk[1], Monika Głuch-Lutwin[3], Barbara Mordyl[3], Bila Abdoul Fatahou Kabore[4], Séverine Morisset-Lopez[4]

[1] Laboratory of Experimental Neuropharmacology, Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna St, 30-688 Krakow, Poland
[2] Doctoral School of Medical and Health Sciences, Jagiellonian University Medical College, 16 Św. Łazarza St, 31-530 Krakow, Poland
[3] Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna St, 30-688 Krakow, Poland
[4] Centre de Biophysique Moléculaire, CNRS UPR 4301, Université d'Orléans, rue Charles Sadron, 45071 Orléans Cedex 2, France

Rapid-acting antidepressants are urgently needed, yet the discovery of new compounds is still often guided by receptor affinity rather than by an understanding of how individual signaling pathways translate into therapeutic-like effects. This is particularly important for multimodal ligands, whose pharmacological profile cannot be fully explained by binding to a single target.

HBK-15 is a multimodal compound with high affinity for serotonin 5-HT_{1A} and 5-HT_7 receptors, dopamine D_2/D_4 receptors, and sigma-1 receptors. What makes HBK-15 especially interesting from a drug discovery perspective is its pathway-selective signaling profile. At the 5-HT_{1A} receptor, HBK-15 preferentially promotes ERK1/2 phosphorylation, while showing no agonist activity in β-arrestin recruitment, cAMP signaling, or calcium mobilization assays. At the 5-HT_7 receptor, the compound also displays pathway-dependent activity, showing partial agonism in cAMP signaling without detectable β-arrestin recruitment. This functional selectivity suggests that HBK-15 may engage specific intracellular mechanisms rather than simply activating or blocking receptor targets in a uniform manner.

Acute administration of HBK-15 produces rapid antidepressant-like and procognitive effects in male mice, making it a useful model compound for exploring how pathway-selective and multimodal pharmacology may translate into behavioral outcomes. Current work focuses on molecular and cellular correlates of these effects, as well as potential sex-dependent differences in pharmacological activity. Particular attention is given to ERK1/2-related signaling as a potential molecular component of the broader multimodal pharmacological profile underlying the rapid behavioral effects of HBK-15.

By integrating receptor binding, pathway-selective signaling, and behavioral pharmacology, this talk will highlight HBK-15 as an example of how multimodal compounds can be evaluated beyond simple target affinity. This approach may help identify signaling signatures associated with rapid antidepressant-like and procognitive activity and guide the development of more mechanism-informed CNS drug discovery strategies.

Evidence before infrastructure: building early-stage biotech companies around the asset

Lucas Rodriguez

Orchid Capital

Early-stage biotechnology companies are often judged by how quickly they begin to resemble mature pharmaceutical organizations: leadership teams, internal functions, facilities, operating infrastructure, and corporate scale. Yet in early biotech, the company itself is not the product. The asset is the product, the evidence package is the value, and the company is the vehicle.

This talk will explore how founders, investors, and development partners can build biotech companies around value-changing evidence rather than premature infrastructure. Drawing on lessons from a career in biotech company-building, including the development and acquisition of CerSci Therapeutics, the presentation will examine how lean operating models, disciplined capital allocation, and expert technical partnerships can move an asset from early promise toward partnerable clinical-stage value.

The discussion will focus on practical questions that matter in early development: what evidence most changes the value of an asset, when should a company build internal capabilities versus access external expertise, how early should business development begin, and how can capital efficiency preserve strategic optionality?

The central message is simple: great biotech companies are not built by spending more. They are built by learning faster. When the right evidence meets the right capital, science has a chance to become medicine.

Serendipity results as a driving force for novel reaction development

Serhiy V. Ryabukhin[1,2,3,4], Volodymyr Voloshchuk[1,4], Sergiy Ivonin[4], Dmytro Volochnyuk[1,2,3,4]

[1] Enamine Ltd., Ukraine
[2] Taras Shevchenko National University of Kyiv, Ukraine
[3] Enamine Scientific Research Institute, Ukraine
[4] Institute of Organic Chemistry, NAS of Ukraine

Serendipity results are evidence that accompanies researchers throughout their careers. We, at Enamine, generated more than 90k experimental data per month from our four synthetic departments (Combinatorial Chemistry, Custom Synthesis, Building Block Synthesis, and Process Chemistry). Of course, these results are not only positive. Most of them are regular negative results that are also useful for optimizing reaction conditions, determining scope, diverse chemoinformatic projects, and machine learning. However, nowadays we have begun to put more and more attention to careful analysis of negative results, especially when these negative results are serendipitous with absolutely unexpected reaction pathways.

In this talk, we will show you several examples of such serendipity-based research that led us to discover novel, unpredictable heterocyclizations. Also, we would demonstrate how we found these reactions, detected their pathways, elaborated preparative procedures, and determined their scope and limitations.

References

1. Ivonin, S. P.; Voloshchuk, V. V.; Stepanova, D. S.; Ryabukhin, S. V.; Volochnyuk, D. M. *ChemRxiv* **2024**, 10.26434/chemrxiv-2024-4ps8d.
2. Ivonin, S. P.; Voloshchuk, V. V.; Rusanov, E. B.; Suikov, S. Yu.; Ryabukhin, S. V.; Volochnyuk, D. M. *Org. Chem. Front.* **2024**,*7*(11), 2088–94.
3. Ivonin, S. P.; Yurchenko, A. A.; Voloshchuk, V. V.; Yurchenko, S. A.; Rusanov, E. B.; Pirozhenko, V. V.; Volochnyuk, D. M.; Kostyuk, A. N. *J. Fluor. Chem.* **2020**, *233*, 109509.

Expansion of the druggable genome, metabolomics resources, drug pleiotropy and interactions

Helgi B. Schiöth

Uppsala University, Sweden
NIRI, Latvia

The landscape of pharmacological drug targets is rapidly expanding as new therapeutic modalities. We analysed large-scale datasets using computational approaches revealing the opportunities within the human proteome for new drug targets. Recent integration of regulatory approvals, clinical trials and multiple drug-target databases demonstrates substantial growth in the number and diversity of targets entering clinical development, although less than 5% of the human proteome is currently targeted by approved drugs. GPCRs, kinases and hydrolases remain major target classes, while membrane-associated and secreted proteins are emerging increasingly as therapeutic opportunities. Multi-omics approaches are changing how drug mechanisms and disease biology can be investigated by integrating genomic, transcriptomic, proteomic and metabolomic information across biological systems. The rapidly growing open-access metabolomics resources, including Metabolomics Workbench and MetaboLights, which provide large collections of metabolite measurements and associated experimental data are important but complicated resources. Systematic integration creates opportunities for large-scale analyses of metabolic signatures of drugs, while also presenting substantial challenges related to data harmonization, metabolite annotation and study heterogeneity. Drug pleiotropy, including repurposing and the ability of pharmacological agents to influence multiple biological pathways and indications are being explored. Together, these developments illustrate how integrated pharmacology, omics and computational analysis can broaden the understanding of the druggable genome and provide new strategies to develop our perception of therapeutic effects, adverse effects and complex chemical interactions.

Metallo-enzymes: mechanisms to medicines

Christopher J. Schofield

Chemistry Research Laboratory and the Ineos Oxford Institute for Antimicrobial Research, University of Oxford, 12 Mansfield Road, OX1 3TA, Oxford, United Kingdom

The lecture will describe how scientific curiosity driven studies on the mechanisms of metallo-enzymes that catalyse reactions presently challenging for synthesis have helped to enable the discovery of new therapies. The particular focus will be on zinc and iron dependent oxygenases involved in antibiotic biosynthesis and resistance, including how work on these led to unexpected new targets for diseases ranging from anaemia to cancer. It will describe time-resolved structural studies on metallo-enzyme catalysis and suggest how these may be useful in drug discovery.

Senolytic nanoplatform to target and eliminate senescent melanoma cells

Solange Selzer[1], Julia Słaby[2], Wojciech Witkowski[3], Anna Lewińska[2], Maciej Wnuk[2], Grzegorz Litwinienko[3], Raluca Fratila[1], Maria Moros[1]

[1] Instituto de Nanociencia y Materiales de Aragón (INMA), CSIC-Universidad de Zaragoza, 50009 Zaragoza, Spain
[2] University of Rzeszow, Rzeszow 35-959, Poland; 3 Faculty of Chemistry, University of Warsaw, Warsaw 02-093, Poland
selzersolange@unizar.es

Skin cancer, namely melanoma and non-melanoma skin cancers, are the most common types of malignancy in the Caucasian population, with a worldwide yearly increasing incidence. The therapeutic alternatives usually employed for cancer treatment can promote stress-induced premature senescence of normal and/or neoplastic cells. These senescent cells are often called zombie cells because they are resistant to cell death and their accumulation may promote tumour recurrence, metastasis or drug resistance. Moreover, they exhibit upregulated expression of heat shock proteins (HSPs), which further enhances their resistance to stress-induced apoptosis and may limit the effectiveness of conventional therapies, including hyperthermia-based approaches[1].

Senolytic drugs such as quercetins are commonly used for killing senescent cells; however, they have low bioavailability and selectivity towards these cells, which can end up producing side effects. Indeed, one of the major challenges to treat senescent cells is the lack of precise markers for their targeting.

Here, we propose an innovative therapeutic approach to eliminate senescent cells by using a multifunctional nanoplatform based on magnetic nanoparticles (MNPs), with the final aim of inhibiting skin cancer progression (Figure 1). MNPs were synthesized via thermal decomposition, incorporating Fe, Mn, and Zn to optimize their magnetic properties. To achieve precise targeting, the MNPs were bioconjugated with an antibody against alpha-integrin (ITAG1), a novel marker for drug-resistant senescent melanoma cells[2]. Furthermore, to induce senolytic activity, the particles were functionalized with a novel thioquercetin derivative exhibiting enhanced efficacy against melanoma cells[3].

The resulting nanoplatform is being evaluated in normal tumoral and senescent skin cells to assess its senolytic potential through selective targeting. Additionally, we are investigating the possibility of using magnetic hyperthermia to improve therapeutic outcomes.

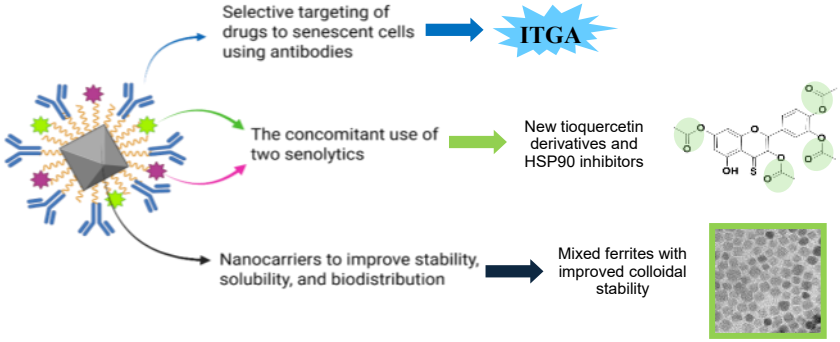


Figure 1. Multifunctional nanoplatform based on magnetic nanoparticles and their novel components.

References

1. Scudellari, M. "To stay young, kill zombie cells" *Nature* 550, 448–450 (**2017**).
2. Słaby, J. et al. "ITGA1, the alpha 1 subunit of integrin receptor, is a novel marker of drug-resistant senescent melanoma cells in vitro" *Arch Toxicol* 99(6), 2611-2625 (**2025**).
3. Słaby, J. et al. "HSP90 inhibition potentiates oxidant-based antimelanoma action of novel thioquercetin derivatives by compromising AhR/CYP1A1 pathway. *Apoptosis* (**2026**).

Respiratory microfold cells – a novel inflammation-induced cell type in human and murine lungs

Abhishek Goswami[1], Katharina Dersch[1], Paul Gueguen[2], Konstantinos Gkelis[1], Christian Urban[2], Karīna Siliņa[1]

[1] Institute of Pharmaceutical Sciences, ETH Zürich
[2] Functional Genomics Center Zurich (FGCZ), University of Zürich & ETH Zürich
karinasilina@pharma.ethz.ch

Mucosal surfaces harbor homeostatic lymphoid organs called mucosa-associated lymphoid tissue (MALT), which ensure immune protection and regulation of microbiota. MALT are surrounded by specialized follicle-associated epithelium (FAE), which contains crucial regulators of mucosal immunity called microfold cells (M cells). M cells are best understood in the gut, where they transcytose luminal antigens to the underlying immune cells, orchestrate immune cell interactions needed for IgA class switching, and participate in antigen presentation to T cells. In contrast to other species, the lower respiratory tract of healthy humans and mice have no MALT or FAE/M cells. Nevertheless, prolonged inflammation induces ectopic lymphoid organs called tertiary lymphoid structures (TLS) in the lungs of both species. We previously observed that TLS in human lung cancer often harbor an atypical epithelial lining[1]. Whether such cells represent FAE/M cells of TLS and what their role in pulmonary immunity is has not been studied.

Here, we employed spatial and single cell multiomics approaches and identified *bona fide* FAE/M cells in the alveolar compartment of inflamed human and murine lungs. M cells developed from the alveolar type 2 cells, expressed multiple immunoregulatory molecules such as CCL20, PD-L1, LTB, and showed high expression of antigen presentation and interferon response pathways suggesting their involvement in the regulation of respiratory immunity. Ongoing work is focused on establishment of *in vitro* and *in vivo* models to study the functional roles of FAE/M cells in respiratory immunity and their therapeutic potential using M cell-targeted vaccine designs.

References

1. Silina, K.; Soltermann, A.; Movahedian Attar, F.; Casanova, R.; Uckeley, Z. M.; Thut, H.; Wandres, M.; Isajevs, S.; Cheng, P. F.; Curioni Fontecedro, A.; Foukas, P.; Levesque, M. P.; Moch, H.; Line, A.; van den Broek, M. Germinal Centers Determine the Prognostic Relevance of Tertiary Lymphoid Structures and Are Impaired by Corticosteroids in Lung Squamous Cell Carcinoma. *Cancer Res* **2018**, *78*, 1308–1320. https://doi.org/10.1158/0008-5472.CAN-17-1987.

Restoration of saccadic eye movements and visually guided behavior in ambient white light with photoswitchable small molecules

Rosalba Sortino

Institute for Bioengineering of Catalonia (IBEC)

Blinding diseases due to degeneration of photoreceptors (PhRs) like geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) and retinitis pigmentosa (RP) leave the rest of the retinal circuitry largely intact, albeit unable to respond to light. Gene therapy has been able to revert PhR degeneration, but it can only be applied to a rare mutation affecting a small subset of RP patients. Alternatively, implanted electronic retinal prostheses aim at a larger population by electrically stimulating the surviving neurons. However, the treatment is invasive, costly, and provides limited resolution. Photopharmacology can develop photoswitchable small molecules to restore vision impairment by conferring light sensitivity to ion channels that are widely expressed in the remaining inner retinal neurons, and a first-in-human clinical trial is ongoing. Here, we have developed novel photoswitchable small molecule ligands of metabotropic glutamate 6 ($mGlu_6$) receptors, which are located exclusively at the dendrites of ON bipolar cells (OBCs, postsynaptic to PhRs) and can leverage a privileged position to mimic physiological signals in the remnant retinal circuit. These photoswitchable ligands (prosthe6) thus act as 'molecular prostheses' that can restore the light input to the retina *via* upstream-targeted control of the circuit after PhRs degeneration. Prosthe6 compounds are allosteric, drug-like, water soluble, and display outstanding *in vitro* properties including full efficacy, nanomolar potency, fast deactivation in ambient white light, and fast reactivation in the dark. *In vivo* experiments show that they readily recover the saccadic eye movements of blinded zebrafish larvae and restore the innate light avoidance behavior in mouse models of blindness (GA and RP). These effects are mediated by $mGlu_6$ receptors *in vivo*. In addition, at least two compounds (prosthe6-**12** and -**15**) can restore sight by topical administration and display promising safety properties to become potential drug candidates for sight restoration in patients with degenerative blinding diseases.

Photopharmacology: towards image-guided pharmacotherapy

Wiktor Szymanski

Department of Medicinal Chemistry, Photopharmacology and Imaging,
Groningen Research Institute of Pharmacy, University of Groningen
w.c.szymanski@rug.nl

Molecular photomedicine holds the promise for precise treatments, which avoid systemic adverse effects and development of drug resistance. This promise is supported by current medical imaging modalities that reveal the nature and location of malignancies. At the same time, biomedical engineering has recently created methods to deliver light deep into human body. The photomedicine puzzle is currently missing its final piece – the way of translating light into a therapy. To address this challenge, drugs are introduced whose activity could be reversibly or irreversibly turned on with light.

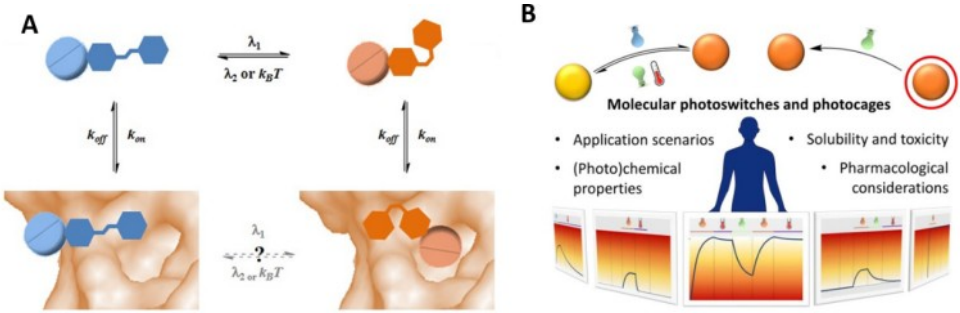


Figure. The principle of photopharmacology (A) and its key molecular tools (B).

The aim of this presentation is to describe the emerging concept of photopharmacology (Figure A) [1], which is currently being developed and applied to precisely control the activity of drugs using light. The presentation will focus on our efforts towards bridging light and medicine, focusing first on new light-operated tools [2] (molecular photoswitches [3] and photocages [4], Figure B). Next, I will highlight the synergies between medical imaging and therapy, offered by light, through photo-responsive optical [5] imaging agents. Finally, using those examples, I will highlight the applications [6] and structural aspects [7] of photopharmacology.

References

1. M. Hoorens et al. *Trends. Biochem. Sci.* **2018**, *43*, 567–575.
2. I. M. Welleman et al. *Chem. Sci.* **2020**, *11*, 11672–11691.
3. F. Cardano et al. *Angew. Chem. Int. Ed. Engl*, **2025**, *64*, e202423506.
4. A. M. Schulte et al. *J. Am. Chem. Soc.* **2022**, *144*, 12421–12430.
5. F. Reeßing et al. *ACS Omega* **2020**, *5*, 22071-22080.
6. D. Kolarski et al. *Nature Comm*. **2021**, *21*, 3164.
7. V. Arkhipova et al. *J. Am. Chem. Soc.* **2021**, *143*, 1513–1520.

Polypeptide-based nanomedicines: enhancing tropism and overcoming biological barriers

María J. Vicent, PhD

Polymer Therapeutics Lab., Príncipe Felipe Research Center (CIPF), 46012 Valencia, Spain,
and CIBERONC, IISCIII, Madrid, Spain
mjvicent@cipf.es

Polypeptides play a pivotal role in various domains, particularly in nanomedicine[1]. The physico-chemical properties and biological performance of polypeptide-conjugates are dictated by a complex interplay of structural factors, highlighting the critical need for detailed structure–activity relationship (SAR) studies to inform the design of hierarchical polypeptide systems. Notably, this structural complexity is advantageous, as even subtle molecular alterations can yield significant and unexpected biological effects[1].

In our research group, we have addressed conventional challenges in polypeptide synthesis through precise, controlled reactions, enabling the creation of well-defined architectures via N-carboxyanhydride (NCA) polymerization[2]. Post-polymerization modifications further extend functionality, introducing a diverse array of orthogonally reactive attachment points[1,3]. Utilizing this modular, bottom-up approach, we have engineered polypeptides with varied architectures, including diblock copolymers and star-shaped constructs – that self-assemble into supramolecular nanostructures. The scale up of such assemblies have been optimised by means of microfluidics, to yield nanocarriers that have demonstrated promising traits, such as tissue specificity[4], subcellular compartment targeting[5], and potential for brain delivery[6].

Coupling this structural strategy with rational crosslinking approaches and polymer–drug linker design[4–7] has enabled extensive in vitro and in vivo evaluation. These systems show minimal toxicity, enhanced cellular uptake, prolonged systemic circulation, and targeted accumulation in specific sites such as lymph nodes[4], mitochondria[5], and the brain[6]. These effects are modulated by structural parameters including stiffness, deformability, charge, size, or shape.

These findings position our polypeptide-based nanosystems as promising candidates for use as nanocarriers in therapeutic and diagnostic applications[8].

Acknowledgements
This work has been supported by European Research Council (ERC-CoG-2014-648831 “MyNano”, Grant ERC-PoC-2018-825798 Polymmune, ERC-PoC-PolyBraint), ITN MSCA (Biomolmacs H2020-MSCA-ITN-2019-850418 and NATPRIME H2020-MSCA-ITN-2023-101168881), Association for Cancer Research (AECC; PRYGN259257VICE-MITONano), the Spanish Ministry of Science and Innovation (PID2023-152459OB-I00), NextGenerationEU (PRTR-C17.I1) Pol@Mets (MFA/2022/065), Foundation Health La Caixa-LCF/PR/HR19/52160021-NanoPanther, HR22-00602-NanoGBA and HR24-00968-PINT and Horizon Europe EU-OPENSCREEN UNLOOC (GA n. 101140192) and IMPULSE (GA No. 101132028). Part of the equipment employed in this work has been funded by Generalitat Valenciana and co-financed with FEDER funds (PO FEDER CV 2014–2020).

References

1. (a) T. Melnyk et al. *Adv. Drug Deliv. Rev.* **2020**, *160*, 136–69; (b) Dordevic S. et al. *Drug Deliv. Trans. Res.* **2021**, 1–26.
2. (a) I. Conejos-Sánchez et al. *Polym. Chem.* **2013**, *4*, 3182–9; (b) Duro-Castaño, A., et al. *Mol. Pharm.* **2015**, *12*, 3639-3649; (c) WO2017025298A1; d) WO2013060919A1.
3. (a) M. Barz et al. *Polym. Chem.* **2013**, 4, 2980–94; (b) S. Dordevic et al. *Small* **2023**.
4. (a) A. Duro-Castaño, et al. *Adv. Mater.* **2017**, 29, 1702888; (b) L.I.F. Moura, A. Malfanti et al. *Adv. Mater.* **2025**, *37*(16), 2417348.
5. a) C. Pegoraro et al. *Adv. Drug Deliv. Rev.* **2024**; (b) Patent application EP23382668.4, 2023; (c) C. Pegoraro et al. *Adv. Mater.* **2025**, 2411595; (d) C. Pegoraro et al. *J. Mater. Chem. B* **2025**, *13*(8), 2658.
6. (a) A. Duro-Castaño et al. *Science Advances* **2021**, *7*, eabf9180; (b) Patent EP22383152.0, 2022. (c) I. Conejos-Sánchez et al *Biomaterials* **2026,** 328, 123867
7. (a) J.J. Arroyo-Crespo, et al. *Biomaterials* **2018**, 186, 8–21; (b) J.J. Arroyo-Crespo, et al. *Adv. Funct. Mater.* **2018**, 28(22), 1800931; (c) P. Boix-Montesinos et al. *J. Control. Release* **2024**.
8. (a) I. Conejos-Sánchez, et al. *Curr. Opin. Biomed. Eng.* **2021**, *20*, 100323. (b) A. Benaicha-Fernández et al. *Adv. Func. Mat.* **2026**, e00080

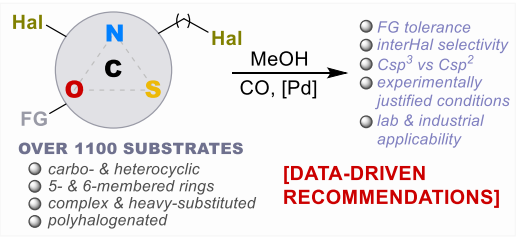
Predictive, regioselective Pd-catalyzed carbonylation as a gateway to privileged carboxylic acid frameworks

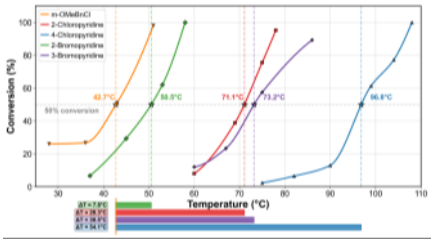
Dmytro Volochnyuk[1,2,3], Vadim Dudko[1,3], Maxim Nechaev[1,3], Dmytro Leha[2,4], Serhiy Ryabukhin[1,2,3]

[1] Enamine Ltd, 78 Winston Churchill str., Kyiv, Ukraine, e-mail: s.v.ryabukhin@gmail.com
[2] Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., Kyiv, Ukraine
[3] Institute of Organic Chemistry, NAS of Ukraine, 5 Academik Kukhar str., Kyiv, Ukraine
[4] Enamine Scientific Research Institute, 78 Winston Churchill str., Kyiv, Ukraine

Among C1 feedstocks, carbon monoxide is especially attractive to be inexpensive, abundant, and versatile one. Yet despite its potential, the direct use of CO in laboratory-scale synthesis has been historically limited by safety concerns, elevated pressure requirements, and the narrow applicability of existing protocols. In this research, we demonstrate the challenges of translating preparative synthetic methodologies from aromatic to diverse heterocyclic rings.

In this report, we will discuss the development of a scalable, regioselective, and broadly applicable Pd-catalyzed methoxycarbonylation methodology that directly employs CO as the carbonyl source under relatively mild and operationally simple conditions. Through the systematic investigation of more than 1100 functionalized substrates (including polyhalogenated (het)arenes, (het)aryl halides with diverse positional isomers, and substrates containing both sp2 and sp3 carbon-halogen bonds) were tested. We formulated general criteria for predicting regioselectivity and substrate applicability. The results revealed the impact of the nature of the halogen atom, the hybridization state of the carbon center, the type of heteroaromatic core, and the substitution environment on the reaction outcome. Overall, the methodology provides efficient and high-yielding access to a wide array of (hetero)arylcarboxylic and (hetero)arylacetic acids, without relying on exotic ligands or CO surrogates.





Development of antibiotics targeting LpxH – a key enzyme in lipopolysaccharide synthesis in Gram-negative bacteria

Edouard Zamaratski

Upsala University

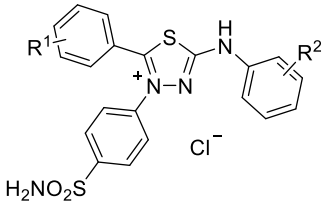
Identification and development of an antibiotic class acting via LpxH, a clinically unexploited target in lipopolysaccharide synthesis will be presented. The lipopolysaccharide synthesis pathway is essential in most Gram-negative bacteria and there is no analogous pathway in humans. Based on a series of phenotypic screens, we identified a hit targeting this pathway that had activity on efflux-defective strains of Escherichia coli. With the help of obtained X-ray structures we designed inhibitors with good activity on wild-type strains. Optimization of properties such as solubility, metabolic stability and serum protein binding resulted in compounds having potent in vivo efficacy against bloodstream infections caused by the critical Gram-negative pathogens E. coli and Klebsiella pneumoniae. Other favorable properties of the series include a lack of pre-existing resistance in clinical isolates, and no loss of activity against strains expressing extended-spectrum-β-lactamase, metallo-β-lactamase, or carbapenemase-resistance genes. Further development of this class of antibiotics could make an important contribution to the ongoing struggle against antibiotic resistance.

2-Aryl-5-(arylamino)-3-(4-sulfamoylphenyl)-1,3,4-thiadiazol-3-ium chlorides as selective carbonic anhydrase VII inhibitors

Morteza Abdoli[1], **Raivis Žalubovskis**[1], **Claudiu T. Supuran**[2]

[1] Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006 Riga, Latvia
[2] NEUROFARBA Department, Pharmaceutical and Nutraceutical Section, University of Florence, Via Ugo Schiff 6, 50019 Florence, Italy

A series of novel 2-aryl-5-(arylamino)-3-(4-sulfamoylphenyl)-1,3,4-thiadiazol-3-ium chlorides, were obtained by reaction of easily accessible *N*-aryl-2-(4-sulfamoylphenyl) hydrazinecarbothioamides with benzoyl chlorides under catalyst- and additive-free conditions (Fig. 1).[1] The newly synthesized mesoionic compounds were tested for the inhibition of four different isozymes of human carbonic anhydrase (hCA I, II, VII and IX, EC 4.2.1.1).



hCA I; K_i: 92.8–8438 nM
hCA II; K_i: 0.6–247.9 nM
hCA VII; K_i: 6.4–79.4 nM
hCA IX; K_i: 41.8–2781 nM

Figure 1. General structures of mesoionic compounds investigated in this study.

The most potent inhibition was observed against hCA II and hCA VII, while hCA I and hCA IX were inhibited less effectively. Among the tested compounds, the derivative bearing R^1 = 4-OMe and R^2 = H emerged as the most potent hCA VII inhibitor, exhibiting a K_i value of 7.2 nM, comparable to that of AAZ. Furthermore, it demonstrated remarkable selectivity for hCA VII, being 685-, 31-, and 35-fold more selective than for hCA I, hCA II, and hCA IX, respectively. These findings suggest that this class of mesoionic compounds constitutes a promising scaffold for the design and development of selective hCA VII inhibitors as potential agents for the treatment/management of neuropathic pain.

Acknowledgements
This work was supported by the European Regional Development Fund (ERDF, project no. 1.1.1.9/ LZP/1/24/014).

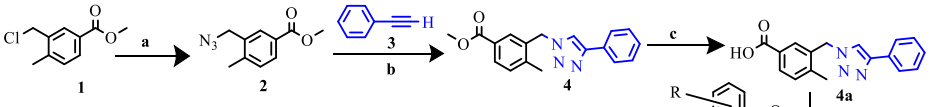
References
1. Sousa-Pereira, D.; Silva de Oliveira, T.; Paiva, R.O.; Chaves, O.A.; Netto-Ferreira, J.C.; Echevarria-Lima, J.; Echevarria, A. *Molecules*. **2020**, *25*, 2537.

Quinoline–triazole hybrids, novelly prepared, are showing potent antimicrobial and antivirulence activities

Manikandan Alagumuthu

Anti-Microbial Research Lab (AMRL), Dept of Microbiology, Saveetha Medical College and Hospital, SIMATS, Chennai-602105, India
mailtomicromani@gmail.com; ORCID: 0000-0002-7065-5884

The rapid emergence of multidrug-resistant Gram-negative pathogens and biofilm-associated infections has intensified the need for antimicrobial agents capable of simultaneously inhibiting bacterial growth and attenuating virulence. In the present study, a series of novel quinoline–triazole hybrids was rationally designed, synthesized, and biologically evaluated as multifunctional anti-infective agents. The target compounds were efficiently synthesized through a modular three-step strategy comprising quinoline scaffold construction, azidation, and Cu(I)-catalyzed azide–alkyne cycloaddition (click chemistry).



Reagents and conditions:
(a) NaN_3 (2.0 equiv), DMF, 70 °C, 6 h;
(b) phenylacetylene (1.2 equiv), $CuSO_4 \cdot 5H_2O$ (5 mol %), sodium ascorbate (10 mol %), t-BuOH/H_2O (1:1), rt, 8 h;
(c) TFA/DCM (1:1), rt, 2 h.

Scheme 1. Route of synthesis of quinoline–triazole hybrids **6a**–**l**

The synthesized hybrids exhibited potent antibacterial activity against clinically relevant Gram-negative pathogens, with minimum inhibitory concentration (MIC) values ranging from 0.0025 to 2.25 µg/mL. Several derivatives displayed bactericidal activity, evidenced by comparable MIC and minimum bactericidal concentration (MBC) values. Notably, the lead compound demonstrated exceptional antibacterial potency (MIC = 0.0025 µg/mL) and an excellent safety profile, with a selectivity index exceeding 50,000 against HEK cells. Beyond growth inhibition, the lead derivatives effectively suppressed quorum sensing and virulence factor production, inhibited biofilm formation by over 85%, and eradicated preformed biofilms by up to 78% at sub-MIC concentrations. Molecular docking with *E. coli* Omp-A (PDB ID: 9FZD) indicated the interaction potential of compound **6a** (Binding Energy = -10.24 kcal/mol) to the target.

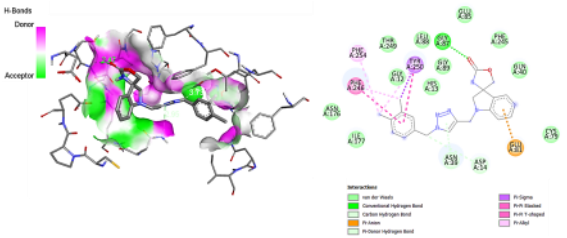


Figure 1. Molecular interaction of compound **6a** with *Escherichia coli* Omp-A (PDB ID: 9FZD).

Mechanistic investigations further revealed enhanced outer membrane permeabilization and increased serum susceptibility, suggesting disruption of outer membrane protein A-mediated membrane integrity. Collectively, these findings establish quinoline–triazole hybrids as promising multifunctional antimicrobial candidates capable of simultaneously targeting bacterial viability, virulence, and biofilm persistence, offering a potential therapeutic strategy against multidrug-resistant Gram-negative bacterial infections.

References
1. Zhang J, Wang S, Ba Y, Xu Z. *Eur J Med Chem*. 2019;174:1-8. doi:10.1016/j.ejmech.2019.04.033
2. Lengerli D, Ibis K, Nural Y, Banoglu E. Expert Opin Drug Discov. 2022 Nov;17(11):1209-1236.

Synthesis and self-assembly of pyridinium betaine- and ylide-containing lipophilic 1,4-dihydropyridines

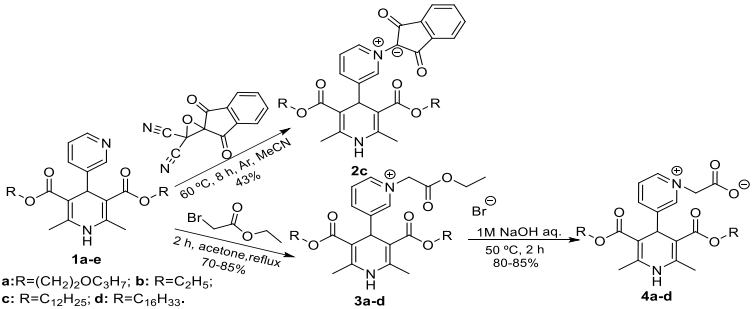
Krista Arule[1,2], Mara Plotniece [2,3], Martins Rucins [1], Reinis Putralis [1,2], Karlis Pajuste [1], Aiva Plotniece [1,2], Arkadij Sobolev [1]

[1] National Institute of Research and Innovation, Riga, Latvia
[2] Riga Stradins University, Faculty of Pharmacy, Riga, Latvia
[3] Institute of Chemistry and Chemical Technology, Faculty of Natural Sciences and Technology, Riga Technical University, Riga, Latvia
krista.arule@niri.lv

N-Heterocycles such as pyridine, 1,4-dihydropyridine, pyridinium, ylide, and betaine derivatives are widely used in medicine, as these structural motifs are found in many drugs.[1] Lipophilic pyridinium-containing 1,4-dihydropyridines (1,4-DHPs) are capable of self-assembling into liposomes and have shown promise as DNA delivery vectors.[2]

The aim of the work: 1) to design and synthesize pyridinium betaine or ylide moiety containing lipophilic 1,4-DHPs; 2) to assess their lipid-like properties and self- assembly behavior through nanoparticle preparation and characterization.

Lipophilic pyridinium betaine- and ylide-containing 1,4-DHPs were synthesized via the Hantzsch reaction followed by pyridine quaternization (Scheme 1).



Scheme 1. Synthesis of 1,4-DHP with pyridinium ylide **4a-d** or betaine **2c** moiety.

Compounds **4b** and **4d** were insoluble in aqueous media. Among the remaining compounds, only betaine **2e** formed stable nanoparticles by ethanol injection (208 nm, PDI 0.143–0.179) and a stable monolayer (MMA 132 Å², compressibility modulus 201 mN/m, collapse pressure 27 mN/m).

Acknowledgements
This work has been supported by the M-ERA.NET 3 project SMARTPIEZO.

References
1. Kerru, N.; Gummidi, L.; Maddila, S. et al. *Molecules* **2020**, *25*, 1909.
2. Pajuste, K.; Hyvonen, Z.; Petrichenko, O. et al. *New J. Chem*. **2013**, *37*, 3062.

Functional enzyme–material interfaces based on immobilized fructosyl peptide oxidase variants for direct HbA1c sensing

Shapla Bhattacharya[1], Lorenzo Basile[1], Alessio Perazzoli[1,2], Leonid Rozanov[1], Anna Lielpētere[1], Alfonso Gautieri[3], Rossella Castagna[1,4], Emilio Parisini[1,2]

[1] Department of Biotechnology, National Research and Innovation Institute, Riga, Latvia
[2] Department of Chemistry "G. Ciamician", University of Bologna, Bologna, Italy
[3] Biomolecular Engineering Lab, Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy
[4] Department of Chemistry, Materials and Chemical Engineering "G. Natta", Politecnico di Milano, Milan, Italy

Diabetes mellitus is a chronic disease that require reliable and affordable strategies for long-term monitoring of glycemic control to prevent severe complications. Glycated hemoglobin (HbA1c) is the gold-standard for detection of long-term glycemia. However, conventional HbA1c assays depend on expensive laboratory infrastructure and specialized personnel. Enzyme-based biosensors offer a promising alternative. Current fructosyl peptide oxidase (FPOX)-based systems detect glycated peptides, but only after a preliminary step of hemoglobin hydrolysis. The goal of this work was the development of FPOX variants able to directly interact with glycated hemoglobin without pretreatment. Using the previously developed X02C mutant as a starting point[1] a combined computational and experimental strategy was implemented[2]. Importantly, one variant, PnFPOX-A14, demonstrated activity toward intact HbA1c[3]. This finding represents a major advance, demonstrating that FPOX enzymes can overcome the limitations through targeted protein engineering. In parallel, immobilization techniques were designed to incorporate engineered PnFPOX-A14 into both colorimetric and electrochemical biosensors. Amino-silanisation of PDMS surfaces allowed covalent immobilization of the enzymes without inactivation. Selective detection of glycated proteins was achieved using electrochemical sensing of hydrogen peroxide, exhibiting low interference from glucose and non-glycated proteins. Collectively, these findings set the base for the future development of advanced HbA1c biosensors.

References

1. Estiri et al. Tailoring FPOX enzymes for enhanced stability and expanded substrate recognition. *Sci Rep*, 2023.
2. Gautieri, A., Rigoldi, F., Torretta, A., Redaelli, A., Parisini, E. In Silico Engineering of Enzyme Access Tunnels. Enzyme Engineering. Methods in Molecular Biology, vol 2397, 2022.
3. A. Perazzoli et al. Structure-guided Engineering of Fructosyl Peptide Oxidase Expands Access to Glycated Protein Substrates, submitted.

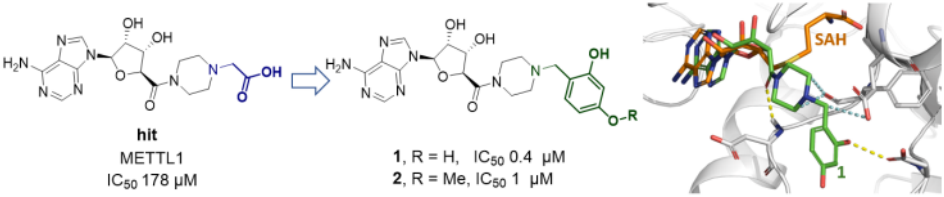
Adenosine 5'-carboxamide containing METTL1 inhibitors

O. Bobileva[1], F. Nai[2], S. Niedrite[1], L. Mayordomo[2], I. Leite[1], A. Caflisch[2]

[1] National Institute of Research and Innovation, Aizkraukles 21, Riga, LV-1006, Latvia
[2] Department of Biochemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland
olga.bobileva@niri.lv

RNA modifications play a critical role in regulating gene expression, cellular stress responses, and the progression of various diseases. Recent studies have demonstrated that dysregulation of RNA modification pathways occurs in human cancers, suggesting that these pathways may serve as promising targets for cancer therapy.[1] *N*7-methylguanosine (m7G) RNA modification influences translation, cell cycle progression, stem cell maintenance, differentiation, and cell migration.[2] The enzyme METTL1 catalyzes the installation of m7G on tRNAs and other RNAs and has been associated with cancer development, tumor growth, and resistance to treatment in several cancer types. Although METTL1 is a SAM-dependent methyltransferase with therapeutic potential, it remains underexplored as a drug target.[3]

This study reports the development of adenosine 5'-carboxamide-containing METTL1 inhibitors. A structure-based optimization strategy was employed, beginning with a previously identified **hit**[4] compound. This approach resulted in the identification of compounds **1** and **2** exhibiting over 170-fold increased potency, with 0.4-1 µM inhibitory activity against METTL1, high selectivity, and favorable kinetic solubility. The binding mode of inhibitor **1** was confirmed by co-crystallization with METTL1, providing evidence that the benzyl group scaffold is accommodated in the guanosine-binding subpocket of METTL1.



Acknowledgements
This work is co-funded by the European Union (European Regional Development Fund) No. 1.1.1.9/LZP/4/26/359.

References

1. Barbieri, I.; Kouzarides, T. *Nat Rev Cancer*. **2020**, 20, 303–322.
2. Zhang, Y.; Xu, W.; Peng, C.; Ren, S.; Mustafe Hidig, S.; Zhang, C. *Cell. Signal.* **2024**, *121* (July), 111288.
3. Bowles, I. E.; Orellana, E. A. *J. Mol. Biol.* **2025**, *437* (16), 169046.
4. Nai, F.; Flores Espinoza, M. P.; Invernizzi, A.; Vargas-Rosales, P. A.; Bobileva, O.; Herok, M.; Caflisch, A. *ACS Bio Med Chem Au*. **2024**, 4 (2), 100–110.

Synthesis of novel PIKfyve-targeting PROTACs for colorectal cancer therapy

Natalia Bosak, Julia Chrzan, Damian Kułaga

Cracow University of Technology, Faculty of Chemical Engineering and Technology, Department of Organic Chemistry and Technology, 24 Warszawska Street, 31-155 Cracow, Poland
natalia.bosak54@student.pk.edu.pl

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains associated with high mortality despite continuous advances in systemic treatment, highlighting the need for the development of novel therapeutic strategies[1]. Among emerging molecular targets, the lipid kinase PIKfyve has attracted increasing attention owing to its role in endosomal trafficking, lysosomal homeostasis and autophagy, biological processes increasingly associated with cancer progression. Despite the promising activity of selective small-molecule PIKfyve inhibitors, limitations such as insufficient *in vivo* stability have prompted the search for alternative PIKfyve-targeting strategies[2]. An alternative approach is offered by proteolysis-targeting chimeras (PROTACs), bifunctional molecules that simultaneously bind a protein of interest and an E3 ubiquitin ligase, resulting in ubiquitination and subsequent proteasomal degradation of the target protein[3]. Compared with conventional small-molecule inhibitors, PROTACs offer several advantages, including enhanced selectivity and improved safety profiles[4]. Among the most widely investigated PROTACs are those employing immunomodulatory imide drugs (IMiDs), such as thalidomide and its derivatives lenalidomide and pomalidomide, to recruit cereblon (CRBN), an E3 ligase substrate receptor that mediates ubiquitination of the target protein[3].

The aim of this project is the design and synthesis of a novel series of PIKfyve-targeting PROTACs based on a previously identified PIKfyve-binding ligand and immunomodulatory imide (IMiD)-derived E3 ligase recruiters. The designed degraders incorporate linkers differing in length and structural features to investigate their influence on the properties of the resulting PROTACs. The synthesized compounds will serve as a platform for future biological evaluation and optimization of targeted protein degraders directed against PIKfyve in colorectal cancer.

References

1. Su, R.; Shao, Y.; Wang, Q.; *et al. J. Mol. Cell Biol.* **2025**, *17*, mjaf027.
2. Li, C.; Qiao, Y.; Jiang, X.; *et al. J. Med. Chem.* **2023**, 66, 12432–12445.
3. Manarin, R.; Frattini, G.; Alonso, V. L.; *et al. Drugs Drug Candidates* **2025**, *4*, 55.
4. Wu, M.; Jiang, Y.; Zhang, D.; *et al. Eur. J. Med. Chem.* **2025**, *282*, 117062.

A new quantitative framework for evaluating size-dependent nanoparticle pharmacokinetics and biodistribution in tumor models

Julija Bulatova[1,2], Baiba Svalbe[1,2], Mingjia Chen[1,2], Antons Sizovs[1,2*]

[1] Laboratory of Pharmaceutical Pharmacology,
The National Research and Innovation Institute
antons.sizovs @niri.lv
[2] Baltic Biomaterials Centre of Excellence,
Headquarters at Riga Technical University

Cancer remains one of the leading causes of death worldwide, and conventional treatments often produce severe side effects. Nanoparticle-based drug delivery offers a way to improve tumor targeting through the Enhanced Permeability and Retention (EPR) effect, in which leaky tumor vasculature and poor lymphatic drainage promote nanoparticle (NP) accumulation.[1,2] Because the efficiency of the EPR effect is believed to strongly depend on NP size, identifying the optimal size is essential for effective NP-based therapies. However, identifying tumor-imposed size restrictions is challenging due to rapid adsorption of serum proteins onto NP surfaces, heterogeneity in tumor vasculature across different types and stages, and limitations of the conventional evaluation methods that requires comparison of multiple treatment groups, resulting in low statistical power of such comparisons.[3–5] To address these challenges, we developed a quantitative method that enables simultaneous measurement of multiple NP sizes within individual biological samples. Using 4T1, LLC and CT26 tumor-bearing mice, we evaluated size-dependent pharmacokinetics and biodistribution, providing a framework for identifying the most effective NP size to exploit the EPR effect in vivo.

Acknowledgements
This work was generously supported by the Eurpean Unions's Horizon 2020 research and innovation programme, Grant No 857287; Latvian Council of Science Fundamental and applied Research Programme Grant lzp-2021/1-593

References
1. Matsumura, Y.; Maeda, H. Cancer Res. **1986**, 46, 6387.
2. Fang, J.; Islam, W.; Maeda, H. Adv. Drug Deliv. Rev. **2020**, 157, 142.
3. Tenzer, S.; Docter, D.; Kuharev, J.; Musyanovych, A.; Fetz, V.; Hecht, R.; Schlenk, F.; Fischer, D.; Kiouptsi, K.; Reinhardt, C.; Landfester, K.; Schild, H.; Maskos, M.; Knauer, S. K.; Stauber, R. H. Nat. Nanotechnol. **2013**, 8, 772.
4. Zhang, J.; Li, H.; Ru, S.; et al. Signal Transduct. Target. Ther. **2026**, 11, 271.
5. Lunova, M.; Smolková, B.; Uzhytchak, M.; Jirsa, M.; Hof, M.; Raška, I.; Šachl, R.; Amaro, M.; Štěpánek, P. J. Controlled Release **2022**, 349, 667.

Implantable platforms for remotely activated therapeutic photobiomodulation

Perazzoli[1,2], S. Torres-Sanchez[3,4,5], E.S. Sánchez García[3,5], I. Suárez-Pereira[3,4,5], E. Opar [6,7,8], T. Hossen[9], N. Ojha[9], L. Petit[9], E. Parisini[1,2], P.Gorostiza[6,7,10], F. Riefolo[11], E. Berrocoso[3,4,5], R. Castagna[1,12]

[1] Department of Biotechnology, National Research and Innovation Institute, Riga, Latvia,
[2] Department of Chemistry "G. Ciamician", University of Bologna, Bologna, Italy
[3] Neuropsychopharmacology & Psychobiology Research Group, Department of Neuroscience, University of Cádiz, Cádiz, Spain
[4]. Ciber of Mental Health (CIBERSAM), ISCIII, Madrid, Spain
[5] Instituto de Investigación e Innovación en Ciencias Biomédicas de Cádiz, INiBICA, Hospital Universitario Puerta del Mar, Cádiz, Spain,
[6] Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute of Science and Technology, Barcelona, Spain
[7] CIBER-bbn (biomaterials, bioengineering, and nanomedicine), Barcelona, Spain
[8] Doctorate Program in Engineering and Applied Science, University of Barcelona, Barcelona, Spain
[9] Photonics Laboratory, Tampere University, Korkeakoulunkatu 3, Tampere, Finland
[10] Catalan Institution for Research Advanced Studies, ICREA, Pg. Lluís Companys 23, Barcelona, Spain
[11] Teamit Institute, Partnerships, Barcelona Health Hub, Barcelona, Spain
[12] Department of Chemistry, Materials and Chemical Engineering "G. Natta", Politecnico di Milano, Milan, Italy

Light-based therapies are emerging as minimally invasive approaches for localized therapeutic modulation, but their application in deep tissues remains limited by the poor penetration of visible wavelengths through biological media. To address this challenge, the PHOTOTHERAPORT project developed implantable platforms based on functional polymer composites incorporating upconverting (UC) particles capable of converting tissue-penetrating near-infrared (NIR) light into localized visible emission. The developed PhotoTheraPorts consist of biocompatible polymer-based matrices loaded with red-emitting UC crystals and engineered for stable implantation and efficient optical performance at the biointerface. Different geometries and architectures were investigated to exhibit strong adhesion to the substrate, mechanical robustness under peeling tests, and uniform luminescence throughout the polymer matrix. Upon external NIR excitation, the implanted materials generated localized red emission, enabling remotely activated light delivery directly at targeted tissue interfaces. The combination of optical conversion capability, mechanical flexibility, low water permeability, and biocompatible encapsulation makes these composites promising candidates for long-term implantable photonic devices. These results demonstrate how multifunctional polymer-UC composites can serve as engineered biointerfaces for minimally invasive phototherapies and photobiomodulation. The integration of upconverting nanomaterials within implantable soft matrices opens new perspectives for the development of remotely controlled therapeutic materials operating in deep biological environments.

Controlling *Pseudomonas aeruginosa* LecB with photoswitchable glycomimetic compounds

Alessio Colleoni[1,2], Shapla Bhattacharya[2,3], Enrico M.A. Fassi[1], Marco De Amici[1], Giovanni Grazioso[1], Carlo Matera[1], Rossella Castagna[2,4], Emilio Parisini[2,5]

[1] Department of Pharmaceutical Sciences, University of Milan, 20133 Milan, Italy
[2] Latvian Institute of Organic Synthesis (LIOS), LV-1006, Riga, Latvia
[3] Faculty of Materials Science and Applied Chemistry, Riga Technical University, Riga, Latvia
[4] Department of Chemistry, Materials and Chemical Engineering Polytechnic of Milan, 20133 Milano, Italy
[5] Department of Chemistry "G. Ciamician", University of Bologna, 40129 Bologna, Italy
carlo.matera@unimi.it, rossella.castagna@niri.lv, emilio.parisini@niri.lv

Antimicrobial resistance (AMR) represents a major global health threat, particularly in hospital-acquired infections where biofilm formation underlies persistent and treatment-refractory bacterial communities. Biofilms provide a protective microenvironment that enhances microbial survival, restricts antibiotic penetration, and promotes horizontal gene transfer. Among key determinants of biofilm development, bacterial adhesion proteins play a central role in initial surface attachment and intercellular interactions, making them attractive targets for novel anti-infective strategies [1].

In this context, we focus on LecB, an outer membrane lectin from *Pseudomonas aeruginosa* that contributes to virulence and biofilm stability through high-affinity carbohydrate recognition. LecB mediates interactions with bacterial surface glycoconjugates and extracellular polysaccharides, thereby supporting adhesion and structural integrity within the biofilm matrix [2].

Here we report the development of novel photoswitchable glycomimetic ligands designed to modulate LecB activity in a light-dependent and reversible manner, enabling spatiotemporal control of bacterial adhesion processes. Building on an initial photoswitchable *hit compound* that demonstrated proof-of-concept LecB targeting, we employed a computationally guided *hit-expansion* strategy to explore chemical space and optimize binding properties. This structure-based approach led to the identification of several improved candidates, showing enhanced affinity in the *cis*-enriched photostationary state compared to the reference compound [3].

Overall, this study highlights the synergy between photopharmacology and computational design in the development of high-affinity, switchable glycomimetics, providing a versatile platform for reversible control of bacterial adhesion and offering promising new avenues for antibiofilm strategies to address AMR.

References

1. Kauser, A.; Parisini, E.; Suarato, G.; Castagna, R. Light-Based Anti-Biofilm and Antibacterial Strategies. *Pharmaceutics***2023**, *15*(8), 2106.
2. Sommer, R.; Hauck, D.; Varrot, A.; Wagner, S.; Audfray, A.; Prestel, A.; Möller, H. M.; Imberty, A.; Titz, A. Cinnamide Derivatives of D-Mannose as Inhibitors of the Bacterial Virulence Factor LecB from *Pseudomonas aeruginosa*. *ChemistryOpen* **2015**, *4*(1), 18–27.
3. Bhattacharya, S.; Tempra, G.; Colleoni, A.; Matera, C.; Castagna, R.; Parisini, E. Synthesis, Photochemical and Biological Evaluation of Novel Photoswitchable Glycomimetic Ligands of *Pseudomonas aeruginosa* LecB. *RSC Adv.* **2025**, *15*, 2025.

Covalent binding of sulfonamides within the ctive Sites of tumor-associated human carbonic anhydrases IX and XII

Vladislava Eimonta[1], Andris Kazaks[1], Daumantas Matulis[2], Kaspars Tars[1], Janis Leitans[1]

[1] National Institute of Research and Innovation, Riga, LV-1006, Latvia
[2] Department of Biothermodynamics and Drug Design, Vilnius University, Vilnius, Lithuania. 7 Saulėtekio Ave, LT- 10257 Vilnius, Lithuania
janis.leitans@niri.lv, vladislava.eimonta@niri.lv

Carbonic anhydrases are widespread metalloenzymes found in many organisms, including humans. Although most isoforms are involved in essential physiological processes, some are associated with various diseases. Among them, the transmembrane human carbonic anhydrase isoforms hCA IX and hCA XII are well-established anticancer drug targets. In this study, we present high-resolution crystal structures of hCA IX and hCA XII in complex with covalent carbonic anhydrase inhibitors. These structures reveal previously undescribed covalent inhibitor binding mechanisms that may facilitate the rational design of isoform-selective inhibitors targeting these clinically relevant enzymes. Although carbonic anhydrases have been drug targets for decades, covalent inhibitors of these enzymes remain poorly characterized, with very few three-dimensional structures currently available in the Protein Data Bank.[1] Our work substantially expands the structural knowledge of covalent carbonic anhydrase inhibitor binding and provides a foundation for the future development of selective anticancer therapeutics.

References

1. Vaškevičius, A.; Baronas, D.; Leitans, J.; Kvietkauskaitė, A.; Rukšėnaitė, A.; Manakova, E.; Toleikis, Z.; Kaupinis, A.; Kazaks, A.; Gedgaudas, M.; Mickevičiūtė, A.; Juozapaitienė, V.; Schiöth, H. B.; Jaudzems, K.; Valius, M.; Tars, K.; Gražulis, S.; Meyer-Almes, F.-J.; Matulienė, J.; Zubrienė, A.; Dudutienė, V.; Matulis, D. *Elife* **2024**, 13, RP101401.

Identification of novel multi-target candidates for TAAR1, SERT, and MAO-B through virtual screening

Milena Dobrowolska[1], Zbigniew Gajda[1,2], Kamil Kuder[1]

[1] Jagiellonian University Medical College in Kraków, Faculty of Pharmacy, Chair of Technology and Biotechnology of Drugs, Medyczna 9 Str., 30-688 Poland
[2] Jagiellonian University Medical College in Kraków, Doctoral School of Medical and Health Sciences, St. Łazarza Str., 31-530, Poland

Central nervous system polypharmacology represents a promising therapeutic approach for treating neurodegenerative diseases accompanied by mood disorders, including Parkinson's disease with comorbid depression. Simultaneous modulation of several monoaminergic systems may lead to improvements in both motor and non-motor symptoms[1]. Trace amine-associated receptor 1 (TAAR1), the serotonin transporter (SERT), and monoamine oxidase B (MAO-B) are protein targets critical for the regulation of dopaminergic and serotonergic neurotransmission, and their combined modulation may represent a promising therapeutic strategy[2,3].

In this study, we performed an *in silico* screening of a proprietary compound library from our research group, focusing on a multi-target profile against TAAR1, SERT, and MAO-B. Utilizing molecular docking, molecular dynamics simulations, and binding free energy calculations, we uncovered ligands displaying favorable interaction profiles with the selected targets. These hits will serve as starting points for future structural optimization and experimental validation.

Acknowledgements
This research was partially funded by statutory funds from the Jagiellonian University Medical College in Kraków – N42/DBS/000385 and was conducted within the framework of Student's Scientific Group "Computer Methods in Drug Discovery".

References

1. Gajda, Z.; Hawrylak, M.; Handzlik, J.; Kuder, K. J. *Int. J. Mol. Sci.* **2024**, *25*(19), 10652.
2. Guan, W. *Curr. Neuropharmacol*. **2025**, *23*(3), 295–308.
3. Raevsky, O. A.; Mukhametov, A.; Grigorev, V. Y.; Ustyugov, A. et al. *Curr. Med. Chem*. **2018**, *25*(39), 5293–5314.

Anticancer and antimicrobial properties of silymarin from milk thistle (*Silybum marianum*): phytochemical analysis and bioactivity evaluation

Mohmmad Asif Gawhari, Prof. Baljinder Kaur

Department of Biotechnology and Food Technology, Punjabi University, Patiala, Punjab, India
mohdasif_rs24@pbi.ac.in

Silymarin is a polyphenolic flavonoid mixture isolated from milk thistle (Silybum marianum) and is responsible for the plant's hepatoprotective effects. Silymarin is a hepatoprotective flavonoid drug available as a biomarker in Silybum marianum. It is used to treat various liver diseases of different origins due to these properties. Phytochemicals are playing a vital role in treating a range of diseases and are used in both traditional and modern medicine. Phytochemical analysis of milk thistle seed extract shows the plant is rich in secondary metabolites, including high levels of total phenolics, flavonoids, and antioxidants. The antibacterial activity of the ethanol seed extract was tested against Gram-positive (Staphylococcus aureus) and Gram-negative (Salmonella enterica) bacteria using a modified Kirby-Bauer disc diffusion technique to determine the zone of inhibition. The results showed that the ethanol seed extract of milk thistle had a strong inhibition zone against both bacteria compared to the control. Additionally, the seed extract demonstrated significant anticancer activity. Milk thistle may be developed into affordable, safe, standardized herbal products and could serve as a source of new broad-spectrum anticancer and antimicrobial agents.

Acknowledgements
I sincerely acknowledge the support and guidance of my supervisor and the Department of Biotechnology and Food Technology, Punjabi University, Patiala, for facilitating my research work. I also express my sincere gratitude to the Indian Council for Cultural Relations (ICCR) for funding my search.

References

1. Kaur, A. K., Wahi, A., Brijesh, K., Bhandari, A., and Prasad, N., 2011. "Milk thistle (*silybum marianum*): A review." *International Journal of Pharma Research and Development*, vol. 3, pp. 1-10.
2. Gurib-Fakim, A. and Mahomoodally, M. F., 2013. "African flora as potential sources of medicinal plants: Towards the chemotherapy of major parasitic and other infectious diseases: A review." *Jordan Journal of Biological Sciences*, vol. 147, pp. 1-8.
3. seeds of silybum marianum against common pathogenic bacteria." *World Journal of Experimental Biosciences*, vol. 3, pp. 36-39.
4. Biosciences, vol. 3, pp. 36-39. Available: https://doi.org/10.13140/RG.2.1.4632.6240 Sayyah, M., Boostani, H., Pakseresht, S., and Malayeri, A., 2010. "Comparison of silybum marianum (l.) gaertn. With fluoxetine in the treatment of obsessive−compulsive disorder." *Progress in Neuro Psychopharmacology and Biological Psychiatry*, vol. 34, pp. 362-365.
5. Waweru, W. R., Osuwat, L. O., and Wambugu, F. K., 2017. "Phytochemical analysis of selected indigenous medicinal plants used in Rwanda." *Journal of Pharmacognosy and Phytochemistry*, vol. 6, pp. 322-324.

For further information, please contact: mohdasif_rs24@pbi.ac.in

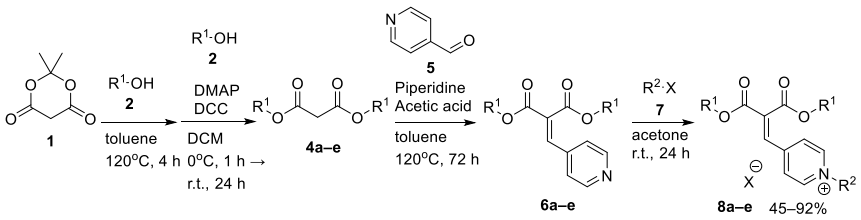
Synthesis and self-assembly properties of malonic acid-derived synthetic lipids

Jevgenijs Harahnins[1,2], Karlis Pajuste[1], Martins Kaukulis[1], Aiva Plotniece[1,2]

[1] National Institute of Research and Innovation, Riga, Latvia
[2] Riga Stradins University, Faculty of Pharmacy, Riga, Latvia
jevgenijs.harahnins@niri.lv

Synthetic lipids are promising materials for nanomedicine due to their tunable structures and ability to self-assembly.[1]

The aim of this work was: 1) synthesis of novel malonic acid-derived synthetic lipids; and 2) preparation and characterization of self-assembled liposomes.



a: R^1=C_2H_5; R^2=CH_3; X=I; **b:** R^1=C_2H_5; R^2=$C_{12}H_{25}$; X=Br; **c:** R^1=C_8H_{17}; R^2=CH_3; X=I;
d: R^1=$C_{12}H_{25}$; R^2=CH_3; X=I; **e:** R^1=$C_{12}H_{25}$; R^2=$C_{12}H_{25}$; X=Br

Scheme 1. General synthetic route to malonic acid-derived synthetic lipids.

A series of malonic acid-derived synthetic lipids were prepared via a multistep synthetic route using adapted previously reported methods.[2–5] The target compounds **8a–e** were obtained in yields ranging from 45% to 92% (Scheme 1) and are proposed as model compounds for potential use in drug delivery.

Liposomes were prepared by ethanol injection of the synthesized lipids in aqueous media.[6] Freshly prepared liposomes had Z-average (Z_{avg}) diameters of 43–173 nm and PDI values of 0.240–0.513. After sample sonication, Z_{avg} diameters ranged 81–280 nm, while PDI values decreased to 0.184–0.458. Stability of liposomes in time will be discussed.

These lipids self-assembled into liposomal structures, supporting their potential as cationic additive in liposomal formulations.

Acknowledgements
Funded by the Latvian Council of Science project lzp-2024/1-0364.

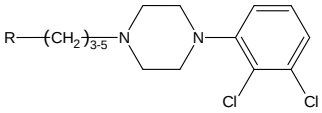
References
1. Mehta, M.; Bui, T. A.; Yang, X. et al. *ACS Mater. Au*. **2023**, *3*, 600.
2. Hosseini, R.; Moosavi, F.; Rajaian H. et al. *Chem. Biol. Drug Des.* **2016**, *88*, 926.
3. Motomura, Y.; Hattori, Y.; Sakurai T. et al. *Macromol.* **2019**, *52*, 4916.
4. Mukherjee, H.; Martinez, C. A. *ACS Catal.* **2011**, *1*, 1010.
5. Vita, F.; Boccia, A.; Marrani A.G. et al. *Chem.–Eur. J.* **2015**, *21*, 15428.
6. Lombardo, D.; Kiselev, *M. A. Pharmaceutics* **2022**, *14*, 543.

Synthesis of new 2,3-dichloroarylpiperazine novels as compounds with potential anticancer activity

Kamil Jurek, Anna K. Drabczyk, Jolanta Jaśkowska

Faculty of Chemical Engineering and Technology, Cracow University of Technology,
24 Warszawska Street, 31-155 Cracow, Poland

Arylpiperazine derivatives have been extensively investigated as therapeutic agents for central nervous system disorders; however, increasing evidence suggests that this privileged scaffold may also represent a valuable platform for anticancer drug discovery. Current research focuses on elucidating the relationship between the structural features of arylpiperazines and their antiproliferative activity. Particular attention has been devoted to the serotonin 5-HT_{1A} receptor, which is overexpressed in several malignancies, including breast and prostate cancers. Among various arylpiperazine motifs, the 2,3-dichlorophenyl-piperazine fragment has emerged as a promising pharmacophore due to its presence in numerous compounds exhibiting significant anticancer activity[1,2], highlighting its potential for the development of novel targeted anticancer agents.



R= NH_2, acetaminophen

Scheme 1. Novels of 2,3-dichloroarylopiperazine derivetives.

Guided by these considerations and the urgent need for novel therapeutic strategies in oncology, a series of new 2,3-dichlorophenylpiperazine derivatives was designed and synthesized. The compounds contained alkyl linkers with three to five carbon atoms and were functionalized with either an amino group or a paracetamol-derived moiety. A microwave-assisted phase-transfer catalysis (MW-PTC) protocol enabled rapid synthesis, reducing the reaction time to only 10 minutes. Preliminary MTT assays on liver cancer cell lines demonstrated promising antiproliferative activity for several derivatives, identifying these compounds as valuable lead structures for the development of novel anticancer agents and providing insights into their structure–activity relationships.

Acknowledgements
This research was supported by the Future Lab PK project, SALIC-FIGHT: Innovative Salicylamide Derivatives in the Fight Against Drug-Resistant Breast Cancer.

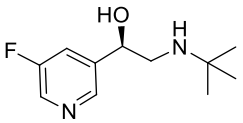
References
1. O'Callaghan LA, et al. Pharmacol Res Perspect. 2025, 13, e70076.
2. Ambrosio M.R. et. al. BMC Cancer 2022, 22, 171.

Pharmacology and signaling of β_2AR modulators – compound 26

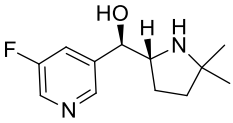
Sofia Karlström[1], Benjamin Pelcman[1], Carina Halleskog[1], Ilga Mutule[2], Linda Supe[2], Krista Jaunsleine[2], Anna Sandström[1], Nodi Dehvari[1], Hamza Bokhari[1], Shane Wright[3], Aikaterini Motso[4], Anastasia Kalinovich[1], Tore Bengtsson[1,4]

[1] Atrogi AB, Sweden
[2] National Institute of Research and Innovation, Latvia
[3] Karolinska Institutet, Sweden
[4] Stockholm University, Sweden
sofia@atrogi.com

Effects on glucose metabolism by β_2-adrenergic receptor (β_2AR) agonists extend beyond local effects in the skeletal muscle and have potential for treatment of a variety of diseases. However, classical β_2AR agonists are of limited use as drugs due to Gs-driven cardiovascular side effects and poor pathway selectivity. GRK2-biased β_2AR activation offers a way to retain metabolic and anabolic benefits while minimizing these liabilities as have been recently discussed.[1] This opens the possibility to use β_2AR agonists for the treatment of disorders with negligible adverse effects due to cAMP mediated signaling. Sustained efficacy can also be achieved due to reduced receptor desensitization compared to classical β_2AR agonists. The next generation, GRK2-biased β_2AR agonists, are promising therapeutic candidates for type 2 diabetes, obesity, sarcopenia, and related metabolic disorders. ATR-258, a GRK2-biased β_2AR agonist has successfully passed phase 1 clinical trials. In here we present a cyclic analogue of ATR-258, Compound 26 (Fig. 1). Properties, synthesis, pharmacology and signaling will be discussed.



ATR-258



Compound 26

Figure 1. Structures of ATR-258 and Compound 26.

References

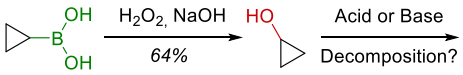
1. Motso. A. et al. *Cell* **2025**, *188*, 5142.

Scalable multi-kilo synthesis and stability-guided handling of cyclopropanol

Kibalnyi M.[1,2], Dmitriv Yu.[1], Leha D.[3,4], Pashenko O.[1,2,3,4], Volochnyuk D.[1,2,3,4], Ryabukhin S.[1,3,4]

[1] Enamine Ltd., Ukraine
[2] Institute of Organic Chemistry of the National Academy of Sciences of Ukraine, Ukraine
[3] Taras Shevchenko National University of Kyiv, Ukraine
[4] Enamine Scientific Research Institute, Ukraine
legus.211288@gmail.com

Cyclopropanol is a valuable strained-ring building block for organic synthesis and medicinal chemistry, but its use remains limited by challenges associated with reproducible scale-up and instability under acidic or basic conditions. This work describes the optimization of a multi-kilo synthesis of cyclopropanol *via* oxidation of cyclopropylboronic acid, combined with stability studies aimed at defining reliable handling conditions. The procedure was improved by extending the post-addition aging of the reaction mixture after hydrogen peroxide dosing from 1 to 18 h at +5 °C, which promoted partial decomposition of residual oxidant and increased the yield by approximately 10%. This modification reduced the amount of sodium thiosulfate required for quenching from 6 kg to 300–350 g, while the hydrogen peroxide charge was decreased by 30% without loss of efficiency. Replacement of diethyl ether with MTBE improved operational safety and enabled solvent recycling; repeated MTBE extraction minimized product losses by accumulating cyclopropanol in the organic phase. Optimization of drying and deep-vacuum distillation using a liquid-nitrogen-cooled receiver increased the isolated yield from about 40% to 64%. Real-time ^{1}H NMR monitoring showed rapid decomposition in CF_3CO_2D and strongly basic aqueous media, slower degradation in KOH/CD_3OD, and high stability in the presence of DBU or DIPEA in DMF for at least three days. These stability data were then used to develop a set of reliable and medicinal-chemistry-relevant protocols for cyclopropanol functionalization, including acylation, sulfonylation, alkylation, and arylation.



System	*k*		Result
CF_3CO_2D	0.0181	38.2 m	mod. dec.
KOH/DMSO-d_6/D_2O	0.0591	11.7 m	fast dec.
KOH/CD_3OD	0.0020	346.5 m	stable
DBU(DIPEA)/DMF	n. d.	>3 d	no dec.

Scheme 1. Synthesis and stability studies of cyclopropanol.

Lowering of long-chain acylcarnitine accumulation reduce disease severity in mouse model of FAOD

Kristaps Krims-Davis[1,2], Edgars Liepinsh[1,2], Baiba Gukalova[1,2].

[1] National Institute of Research and Innovations,
Laboratory of Pharmaceutical Pharmacology, Aizkraukles Str. 21, Riga, Latvia
[2] Riga Stradins University, Dzirciema Str. 16, Riga, Latvia

Fatty acid oxidation disorders (FAODs) are inherited metabolic conditions caused by abnormalities in mitochondrial β-oxidation or the acylcarnitine transport system. These impairments result in the buildup of long-chain acylcarnitines, which can affect cytosolic and mitochondrial enzymes, ion channels, and cellular signaling pathways, making them key drivers of metabolic crises. We established a new non-genetic animal model of FAOD and used it to test a therapeutic approach designed to lower the accumulation of long-chain acylcarnitines.

Pharmacological inhibition of CPT2 was induced in C57BL/6 mice by administration of aminocarnitine (emeriamine), which is metabolized by CPT1 to palmitoyl-aminocarnitine, a potent CPT2 inhibitor. Treatment with aminocarnitine at 6 mg/kg for 14 days caused marked accumulation of long-chain acylcarnitines in all tissues examined, with levels increasing 2- to 10-fold compared with controls. In metabolic phenotyping cages and forced running tests, aminocarnitine-treated mice showed impaired exercise tolerance, running approximately 3-fold shorter distances than control mice. Aminocarnitine also induced hypoketotic hypoglycemia following fasting periods longer than 4–6 hours. At a higher dose (8 mg/kg), it produced severe clinical signs and cardiac complications, leading to humane endpoint criteria after 2–3 daily doses. Furthermore, aminocarnitine treatment elevated plasma ALAT and urea levels, indicating potential liver and kidney damage. Mitochondrial respiration assays in muscle fibers showed 25–28% lower oxidation rates for fatty acids, pyruvate, and succinate in the aminocarnitine-treated group. To determine whether reducing long-chain acylcarnitine accumulation is beneficial, we used Tmlhe heterozygous (+/−) mice. In these mice, aminocarnitine treatment caused a smaller increase in long-chain acylcarnitines and a milder phenotype. Compared with aminocarnitine-treated wild-type mice, Tmlhe+/− mice did not develop hypoglycemia, showed preserved mitochondrial function, and ran distances comparable to untreated control mice.

In conclusion, aminocarnitine treatment provides a valuable non-genetic animal model that recapitulates key manifestations of FAOD. These findings support the concept that long-chain acylcarnitine accumulation is pathogenic and suggest that lowering their levels may help reduce disease severity in patients with FAOD.

Biochemical databases for drug discovery: a crowd-reviewed evaluation of data quality, integration, and usability

Andrii V. Kyrsanov[1,2], Ihor V. Tkachenko[1], Nataliia A. Shtil[1], Duncan B. Judd[4], Konstantin S. Gavrilenko[1,2], Olexandr Ye. Pashenko[1,2,3,5], Dmytro M. Volochnyuk[1,2,3,5], Serhiy V. Ryabukhin[1,2,5]

[1] Enamine Ltd, 78 Winston Churchill str., Kyiv, Ukraine
[2] Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., Kyiv, Ukraine
[3] Institute of Organic Chemistry, NAS of Ukraine, 5 Academik Kukhar str., Kyiv, Ukraine
[4] Awridian Ltd Stevenage Bioscience Catalyst, Gunnelswood Road, Stevenage Herts., UK. SG12FX
[5] Enamine Scientific Research Institute, 78 Winston Churchill str., Kyiv, Ukraine

Progress in drug discovery fundamentally relies on high-quality biochemical data and strong computational tools. The success of these efforts is closely linked to how well the databases supporting medicinal chemistry research perform. This study offers a systematic review of key biochemical databases through a crowd-reviewed approach, evaluating their practical usefulness in drug discovery processes. Students and researchers were surveyed to measure data coverage, search features, and the level of integration between chemical and biological information.

The evaluated databases included ChEMBL, DrugBank, Reaxys, and others, with assessments based on structured queries involving both chemical compounds and protein targets. Our analysis revealed significant variability in data accessibility and reliability across platforms. Academic databases, although broad in scope, often showed inconsistent data quality and inefficient search interfaces. Commercial platforms such as Reaxys offered detailed and well-curated data but required paid subscriptions, limiting their accessibility. Vendor-specific databases, like MedChemExpress, provided targeted product-level information but lacked the broader chemical and biological context needed for comprehensive research.

A key finding was the poor integration of chemical and biological data—a capability essential for effective drug discovery. Many databases do not adequately connect compounds to their biological targets, making multi-parameter analyses more difficult. Additionally, incomplete or incorrect entries can undermine the accuracy of predictive models, reducing the reliability of machine learning and virtual screening workflows.

To address these issues, we suggest specific improvements in database architecture, especially focusing on strengthening the connection between chemical and biological datasets. Databases should feature more user-friendly interfaces and improved search capabilities. Integrating predictive modeling tools into database platforms, supported by carefully curated datasets, could significantly speed up drug discovery processes.

Our crowd-reviewed approach highlighted usability issues faced by users with different skill levels. Although database features have improved a lot, important gaps still exist, especially in user experience and cross-domain data integration. Fixing these problems can enhance data access, analytical processes, and decision-making in drug discovery, leading to faster and more efficient therapeutic development.

Novel SIRT1 modulators and their pharmacological activity

V. V. Lipson[1,3], V. M. Vakula[1,2], N. S. Krasova[2], A. V. Kyrychenko[1,3], S. V. Kovalenko[1], S. M. Desenko[1], A. V. Borisov[4], P. O. Borisko[4], S. O. Zozulya[4]

[1] Institute of Functional Materials Chemistry, State Scientific Institution "Institute for Single Crystals" National Academy of Science of Ukraine, 60 Nauky Ave., Kharkiv, 61072
[2] State Institution "V. Ya. Danilevsky Institute for Endocrine Pathology Problems", National Academy of Medical Sciences of Ukraine, Kharkiv, Ukraine, Alchevsky str.,10, Kharkiv, 61002
[3] V.N. Karazin Kharkiv National University, 4 Svobody Sq., Kharkiv, 61022, Ukraine
[4] Enamine Ltd., Winston Churchill str., 67, Kyiv, 02094, Ukraine
lipson@ukr.net

SIRT1 is a NAD^+-dependent deacetylase enzyme from the family of Silent Information Regulators (Sirtuins), which catalyzes the deacetylation of proteins in different subcellular compartments. The primary function of SIRT1 is the deacetylation of histones H3, H4, and H1. That is why it belongs to the epigenetic factors which affect the functional activity of genes without altering the primary structure of their DNA. This enzyme plays an essential role not only in regulation of gene expression, genome stability main-tenance, but also in apoptosis, autophagy, proliferation, aging, and tumorigenesis. Despite the large number of substrates (more than 50), modulation of SIRT1 activity is considered as a promising strategy for treating metabolic disorders accompanied by diabetes mellitus type 2 (T2DM), cancer, neurodegenerative, and inflammatory diseases. In this report, we present the results of the synthesis of a series of imidazole derivatives, N-acylhydrazones, coumarin chalcones and 2,3-dihydro-1,5-benzodiazepi-nes, among which both inhibitors and activators of SIRT1 were identified using docking calculations and high-throughput screening. Despite some structural similarity with the known imidazothiazole-based SIRT1-activators, such as SRT1460 and SRT1720, our synthesized derivatives 4-imidazo-[1,2-*a*]pyridin-2-ylbenzene-1,2-diol hydrochloride and 4-imidazo[2,1-*b*][1,3]thiazol-6-ylbenzene-1,2-diol hydrochloride showed signifi-cant inhibiting activity (up to 98-100%) of SIRT1. 3-[(2*E*)-3-(1,3-dimethyl-1*H*-pyrazol-4-yl)prop-2-enoyl]-7-hydro-xy-2*H*-chromen-2-one exhibited the same SIRT1 inhibiting activity level. At the same time 2,4-disubstituted 2,3-dihydro-1*H*-1,5-benzodiazepines were superior activators. Using molecular docking against hSIRT1, we found that the identified activators fit perfectly within a hydrophobic pocket of the allosteric site. Within the pocket, they are anchored by a critical conventional hydrogen bond to Asp226 and stabilized by π-alkyl interactions with Ile227. Beyond these structural studies, we evaluated the antidiabetic potential of the new 1,5-benzodiazepine derivative (pyrabentin) in several rat models of T2DM. The effectiveness of pyrabentin under 8-week oral administration at 100 mg/kg *per os* in reducing glucose intolerance, insulin resistance, and obesity in animals with the metabolic memory model at the level of action of the comparator drug metformin has been proven.

Pridopidine in Huntington's disease: PROOF-HD trial findings and 2-year follow-up

May Meltzer[1], Andrew M. Tan[1], Ralf Reilmann[2], Andrew Feigin[3], Anne Rosser[4], Sandra Kostyk[5], Kelly Chen[1], Michal Geva[1], Michael R Hayden[1,6]

[1] Prilenia Therapeutics B.V., Naarden, The Netherlands
[2] George Huntington Institute, Muenster, Germany
[3] NYU Langone Health, New York, NY, USA
[4] University of Cardiff, Cardiff, Wales, UK
[5] Ohio State University College of Medicine, Columbus, OH, USA
[6] CMMT, University of British Columbia, Vancouver, Canada.

Huntington's disease (HD) is a progressive neurodegenerative disorder with no approved disease-modifying treatments. Sigma-1 receptor (S1R) activation modulates pathways implicated in HD, including cellular stress, calcium homeostasis, and mitochondrial function. In the Phase 3 PROOF-HD trial (NCT04556656), pridopidine, a selective S1R agonist, did not meet primary or key secondary endpoints in the overall population, but a predefined subgroup not receiving antidopaminergic medications (ADMs) showed favorable effects on disease progression, cognition, motor function, and quality of life.

To assess whether the benefits observed in off-ADM participants during the double-blind phase of PROOF-HD were sustained during up to 2 years of treatment in the open-label extension (OLE).

PROOF-HD was a randomized, double-blind, placebo-controlled Phase 3 trial of pridopidine, followed by an open-label extension (OLE). Long-term outcomes (up to 2 years) in participants not receiving ADMs were compared with matched external controls from ENROLL-HD and TRACK-HD using propensity score weighting. Disease progression was assessed across functional (TFC), global (cUHDRS), cognitive (SWR), and motor (Q-Motor, TMS) endpoints to evaluate the durability of effects observed during the double-blind phase.

At Week 104, comparisons with matched natural history cohorts extended findings from the PROOF-HD off-ADM subgroup, demonstrating clinically meaningful slowing of disease progression with pridopidine. Effects included slower decline in TFC (62–65%, $p<0.005$), cUHDRS (59–63%, $p<0.0001$), SWR (81–89%, $p<0.0004$), Q-Motor finger-tapping (78%, $p<0.0001$), and TMS (37–63%, $p=0.02$). Overall, pridopidine was associated with slower progression across all outcomes.

Pridopidine benefits across key disease measures were sustained over two years and differed from matched external controls. These findings are being evaluated in the Phase 3 PRECISE-HD trial.

References

1. Reilmann R, Feigin A, Rosser AE, Kostyk SK, Saft C, Cohen Y, et al. Pridopidine in early-stage manifest Huntington's disease: a phase 3 trial. *Nat Med*. 2025;31(11):3780-9.
2. Reilmann R, Tan AM, Rosser AE, Chen K, Anderson KE, Kostyk SK, et al. Long-Term Slowing of Progression in Huntington's Disease with Pridopidine Treatment. *medRxiv*. 2026:2026.02.13.26345490.

Pridopidine protects ALS patient-derived neural progenitor cells by reducing ER stress and restoring mitochondrial function via sigma-1 receptor activation

May Meltzer[1], Randal Hand[1], Andrew M. Tan[1], Maya Shefler[2], Noam Tzuri[2], Rachel G. Lichtenstein[2], Michal Geva[1], Michael R. Hayden[1,3]

[1] Prilenia Therapeutics B.V., Naarden, The Netherlands
[2] Department of Biotechnology Engineering, Ben Gurion University, Israel
[3] CMMT, University of British Columbia, Vancouver, Canada

ER stress and impaired ER–mitochondria signaling contribute to ALS pathogenesis. The sigma-1 receptor (S1R), a chaperone at mitochondria-associated membranes (MAMs), regulates cellular homeostasis and survival. Pridopidine, a selective S1R agonist, has shown neuroprotective and potential clinical benefits in ALS.

To evaluate whether pridopidine reduces ER stress and enhances neuronal survival in sporadic ALS patient-derived neural progenitor cells (NPCs).

Human iPSC-derived NPCs from a sporadic ALS patient were exposed to tunicamycin (1.25 μM, 16 h) to induce ER stress. Cells were treated with pridopidine (0.1–1 μM) ± the S1R competitive antagonist NE-100. ER stress markers (BiP, CHOP), mitochondrial membrane potential (MMP), apoptotic signaling (BAX expression, caspase-3 activation), and cell viability were assessed using flow cytometry, qPCR, and confocal microscopy.

ER stress increases expression of BiP and CHOP, key regulators of the unfolded protein response. In ALS NPCs experiencing ER stress, pridopidine (1uM) significantly reduced BiP (57%, $p<0.0001$) and CHOP (50%, $p<0.0001$) expression levels. Pridopidine also restored mitochondrial membrane potential (up to 47% increase), reduced apoptotic signaling (decreased BAX expression and caspase-3 activation), and improved survival (58% increase, $p<0.0001$) relative to controls. These effects are attenuated by the S1R antagonist NE-100.

These findings highlight pridopidine's potential to enhance neuronal survival in a human ALS model. The potential clinical benefit of pridopidine is being evaluated in PREVAiLS, a randomized, placebo-controlled Phase 3 study in subjects with early (<18 months), definite/probable ALS.

References

1. Meltzer M, Zamir MS, Tzuri N, Tan AM, Geva M, Hayden MR, Lichtenstein RG. Pridopidine Protects ALS Patient-Derived Neural Progenitor Cells via Sigma-1 Receptor Activation. *International Journal of Molecular Sciences*. (in press)

Pridopidine, a sigma-1 receptor agonist, modulates cellular stress and survival pathways across neurodegenerative models

May Meltzer[1], Andrew M. Tan[1,2], Noga Gershoni Emek[1], Michal Geva[1], Michael R. Hayden[1,3]

[1] Prilenia Therapeutics BV, Naarden, The Netherlands
[2] Department of Neurology, School of Medicine, Yale University, New Haven, USA
[3] CMMT, University of British Columbia, Vancouver, Canada

Pridopidine is a potent and selective sigma-1 receptor (S1R) agonist in clinical development for Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). The S1R is an endoplasmic reticulum-resident chaperone enriched at mitochondria-associated membranes (MAMs), where it regulates key processes involved in neuronal survival, including ER stress responses, mitochondrial function, calcium signaling, and protein homeostasis.

To evaluate how pridopidine modulates key cellular pathways involved in neurodegenerative diseases.

The effects of pridopidine were evaluated across multiple experimental systems, including in vitro neuronal models, patient-derived cells, and in vivo models of neurodegenerative disease, as well as clinical studies in HD and ALS.

Across multiple models, S1R activation by pridopidine restored pathways disrupted in neurodegenerative diseases. In HD systems, pridopidine reduced ER and oxidative stress, restored calcium homeostasis, and improved mitochondrial function. In ALS models, it enhanced autophagy, improved neuromuscular junction activity, rescued BDNF transport, and supported motor neuron survival. Pridopidine also improved synaptic function, increased BDNF secretion, restored synaptic plasticity, and preserved dendritic spine density. Neuroprotective effects were confirmed in HD (YAC128, R6/2) and ALS (SOD1) mouse models, showing the biphasic dose-response characteristic of S1R agonists. Clinical findings in HD and ALS provide translational support for these mechanisms.

These findings support a central role for S1R activation in modulating interconnected cellular pathways underlying neurodegeneration. Pridopidine's multimodal mechanism of action supports its continued evaluation as a potential disease-modifying therapy across neurodegenerative and neurodevelopmental disorders.

References

1. Gershoni Emek N, Tan AM, Geva M, Fekete A, Abate C, Hayden MR. Pridopidine, a Potent and Selective Therapeutic Sigma-1 Receptor (S1R) Agonist for Treating Neurodegenerative Diseases. Pharmaceuticals (Basel). 2025;18(12).

Targeting long-chain acylcarnitines as a therapeutic strategy for mitochondrial dysfunction in HMGCR-deficient mice

Anna Miteniece[1,2], Maija Dambrova[1,3], Liga Zvejniece[1], Melita Ozola[1], Baiba Svalbe[1], Helena Cirule[1], Stanislava Korzh[1], Baiba Gukalova[1,3], Kristaps Krims-Davis[1,3], Edgars Liepinsh[1]

[1] National Institute of Research and Innovation, Riga, Latvia
[2] University of Latvia, Riga, Latvia, [3]Riga Stradins University, Riga, Latvia

HMG-CoA reductase (HMGCR) is a key enzyme in cholesterol and isoprenoid biosynthesis and the primary target of statins, widely used for the prevention and management of cardiovascular disease[1]. Despite their efficacy, statin-associated adverse effects can limit treatment adherence, while the underlying metabolic mechanisms, particularly in the liver and muscle, remain incompletely understood[2]. To investigate the consequences of reduced HMGCR activity, we used a tamoxifen-inducible, whole-body *Hmgcr* knockout (KO) mouse model and evaluated whether mevalonate supplementation or pharmacological lowering of long-chain acylcarnitines (LCACs) with methyl-GBB could rescue the resulting phenotype.

Hmgcr-KO mice developed severe metabolic disturbances and lethal liver injury, accompanied by impaired mitochondrial β-oxidation and respiration and marked accumulation of long-chain acylcarnitines and long-chain 3-hydroxy-acylcarnitines. Treatment with methyl-GBB markedly improved survival, prevented hypoglycemia, reduced liver injury, preserved mitochondrial respiratory function, and normalized hepatic LCAC profiles. In contrast, mevalonate supplementation did not rescue the phenotype and increased several acylcarnitine species.

These findings demonstrate that HMGCR deficiency profoundly disrupts mitochondrial fatty acid metabolism and support LCAC accumulation as a mechanistically relevant contributor to HMGCR deficiency-induced toxicity. Pharmacological lowering of LCACs may therefore represent a promising strategy for mitigating metabolic disturbances associated with reduced HMGCR activity.

Acknowledgements
This work was funded by the Latvian Council of Science, grant No. LZP-2023/1-0287. The authors acknowledge the access to the infrastructure and expertise of the Baltic Biomaterials Centre of Excellence (BBCE) (European Union's Horizon 2020 Framework Programme under Grant Agreement No. 857287).

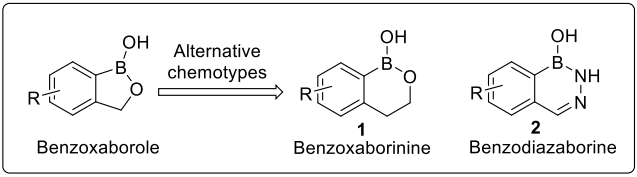
References
1. Zeng, W.; et al. *J. Adv. Res.* **2024**, *76*, 781–797.
2. Liepinsh, E.; et al. *Br. J. Pharmacol.* **2024**, *181*, 2750–2773.

Boron-containing heterocycles: promising chemotypes for targeted carbonic anhydrase inhibition

A. Nikitjuka[1,2], S. Giovannuzzi[2,3], A. Angeli[3], M.-L. Massardi[4], M. Turati[4], R. Ronca[4], A. Bonardi[3], A. Nocentini[3], M. Ferraroni[5], C. T. Supuran[3], J.-Y. Winum[2]

[1] National Institute of Research and Innovation, Aizkraukles iela 21, Rīga, LV-1006, Latvija
[2] IBMM, University of Montpellier, CNRS, ENSCM, 34293 Montpellier, France
[3] Department of NEUROFARBA - University of Florence, 50019, Firenze, Italy
[4] Department of Molecular and Translational Medicine, University of Brescia, 25123 Brescia, Italy
[5] Department of Chemistry "Ugo Schiff", University of Florence, 50019, Sesto Fiorentino. Firenze, Italy
anna.nikitjuka@niri.lv

Uncontrolled cellular proliferation drives the growth of solid tumors, frequently resulting in hypoxic regions. To adapt to these conditions, cancer cells activate abnormal survival pathways.[1] Hypoxia often upregulates biologically active enzymes, most notably transmembrane carbonic anhydrases (CAs). While boron-containing compounds such as benzoxaboroles (*e.g.*, tavaborole, crisaborole) have successfully achieved clinical approval, exploring alternative boron-based chemotypes remains a promising approach in medicinal chemistry.[2]



Through a systematic structure-optimization approach, we identified benzoxaborinine **1** derivatives that demonstrate potent inhibition across various CA isoforms.[3] Our results highlight boron-containing heterocycles **1**and **2** as a compelling platform for designing novel anti-cancer agents, underscoring the broader therapeutic potential of boron chemistry. Ultimately, this work provides a strong foundation for developing targeted CA inhibitors for anti-cancer treatment.

References

1. Z. Chen, F. Han, *et. al.* Signal Transduction Targeted Ther. **2023**, *8*, 70.
2. S. Giovannuzzi, A. Nikitjuka, *et. al. Bioorg Chem.* **2024**, *143*, 106976.
3. S. Giovannuzzi, A. Nikitjuka, *et. al. J. Med. Chem.* **2024**, *67*, 18221.

Linking cognition and neuroprotection: dual 5-HT$_6$R/RIPK1 modulators for Alzheimer's disease

Julia Pakulska[1,2], Magdalena Hawrylak[1,2], Kinga Czarnota-Łydka[1,2], Alicja Szymanek[1], Barbara Mordyl[3], Monika Głuch-Lutwin[3], Grzegorz Satała[4], Małgorzata Więcek[1], Sabina Podlewska[4], Jadwiga Handzlik[1]

[1] Chair of Chemical Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland
[2] Doctoral School of Medical and Health Sciences, Jagiellonian University Medical College, Św. Łazarza 15, 31-530 Kraków, Poland
[3] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków, Poland
[4] Department of Medicinal Chemistry, Jerzy Maj Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Kraków, Poland
julia.pakulska@doctoral.uj.edu.pl

The serotonin 5-HT$_6$ receptor (5-HT$_6$R) is considered an attractive biological target in the search for novel therapeutics for Alzheimer's disease (AD), primarily due to its predominantly CNS-restricted expression and high density in brain regions involved in cognition, such as the hippocampus and prefrontal cortex. Although preclinical studies with 5-HT$_6$R ligands have shown promising cognitive-enhancing effects, these results have not yet translated into clinical success [1]. This highlights the limitations of selective receptor modulation in addressing the multifactorial nature of neurodegenerative diseases such as AD. Consequently, current research efforts increasingly focus on poly-pharmacological strategies that not only improve cognitive symptoms but may also slow or prevent neurodegenerative processes.

In line with this concept, our recent work focuses on the development of dual modulators targeting both 5-HT$_6$R and RIPK1 kinase, a key regulator of the necroptosis pathway implicated in neuroinflammation and neurodegeneration [2]. An interesting design strategy involved the incorporation of a pyrazole scaffold into previously identified 1,3,5-triazine-based selective 5-HT$_6$R antagonists.

The aim of this study was to evaluate the influence of pyrazole topology, substitution pattern, and linker type on the dual 5-HT$_6$R/RIPK1 modulation profile. The research encompassed the synthesis of target compounds via a one-pot organic synthetic approach, *in vitro* assessment of 5-HT$_6$R affinity and RIPK1 inhibitory activity, as well as computer-assisted structure–activity relationship (SAR) analysis.

Acknowledgements
This research was partially funded by the National Science Centre, Poland (grant UMO-2023/51/B/NZ7/02177).

References
1. Czarnota-Łydka et al., Eur. J. Med. Chem.2025, 298, 118026.
2. Shi, K.et al., J Med. Chem. 2018, 61, 1895−1920.

Discovery and development of GRK2-biased β_2AR agonists for the treatment of metabolic disorders

Benjamin Pelcman[1], Carina Halleskog[1], Sofia Karlström [1], Ilga Mutule[2], Linda Supe[2], Anna Sandström[1], Anastasia Kalinovich[1], Nodi Dehvari[1], Hamza Bokhari[1], Darko Mitrovic[3], Tore Bengtsson[1,4]

[1] Atrogi AB, Sweden
[2] National Institute of Research and Innovation, Latvia
[3] Dioclea Labs, Sweden
[4] Stockholm University, Sweden
benjamin@atrogi.com

Biased agonism at G protein–coupled receptors (GPCRs) enables selective modulation of intracellular signaling pathways, offering a strategy to enhance efficacy and safety. Typically, biased agonism indicates the interaction of intracellular portions of the trans-membrane protein with either G-proteins or b-arrestins, manifesting in divergent signaling pathways and physiological effects. We have discovered that another pathway exists for the beta2-adrenergic receptor (β_2AR), wherein the C-terminal part of the protein engages with G protein receptor kinases (GRK's). The downstream signaling leads to translocation of intracellular glucose transporters (GLUT4) to the cell-membrane and uptake of blood-glucose into skeletal muscle cells. This opens up the possibility to use β_2AR agonists for the treatment of disorders with negligible adverse effects due to cAMP mediated signaling and sustained efficacy due to reduced receptor desensitization. Utilizing this concept, we have designed and synthesized compounds that show excellent effects in rodent models of type 2 diabetes, obesity and muscle wasting. One of the compounds, ATR-258, has successfully passed phase 1 clinical trials.

Reference

Motso. A. et al. *Cell* **2025**, *188*, 5142.

Targeting PDE4D: design, synthesis and biological evaluation of novel catechol-based inhibitors

Alessio Perazzoli[2,3], Federica Rapetti[1], Matteo Massa[1], Matteo Lusardi[1], Olga Bruno[1], Lorenzo Basile[2], Shapla Bhattacharya[2], Giulia Abate[4], Sara Anna Bonini[4], Chiara Brullo[1], Emilio Parisini[2,3]

[1] Department of Pharmacy, Section of Medicinal Chemistry, University of Genova, Viale Benedetto XV 3, 16132, Genova, Italy
[2] National Institute of Research and Innovation, Aizkraukles iela 21, LV, 1006, Riga, Latvia
[3] Department of Chemistry "G. Ciamician", University of Bologna, Via P. Gobetti 85, 40129 Bologna, Italy
[4] Department of Molecular and Translational Medicine, Division of Pharmacology, University of Brescia, 25123 Brescia, Italy

Phosphodiesterase 4D (PDE4D) has emerged as a promising therapeutic target, particularly for the treatment of different neurodegenerative disorders. In this study, a novel series of catechol-based PDE4D inhibitors was designed, synthesized, and biologically evaluated to explore the effect of replacing the pyrazole core of the reference compound GEBR-32a with alternative heterocyclic scaffolds. Specifically, new imidazole and pyrrole derivatives were developed to investigate the role of the heterocyclic nucleus in modulating PDE4D inhibitory activity.

The compounds were synthesized through multistep synthetic procedures and tested against the PDE4D catalytic domain. Structure–activity relationship (SAR) studies revealed that replacement of the pyrazole ring with a pyrrole scaffold resulted in a complete loss of activity, whereas imidazole derivatives retained moderate inhibitory potency. Among the synthesized compounds, derivative 2a emerged as the most active inhibitor. SAR analysis highlighted the importance of both the heterocyclic core and the amide side-chain length. The crystal structure of 2a bound to PDE4D revealed productive binding within the catalytic pocket and a distinctive hydrogen-bond interaction between the imidazole N2 atom and a water molecule in the Zn^{2+} coordination sphere, indicating that this additional interaction provides enhanced stabilization. Preliminary cytotoxicity studies on SH-SY5Y human neuroblastoma cells showed no significant toxic effects of 2a s. Overall, the obtained results identified imidazole derivative 2a as a promising starting point for the future development of novel PDE4D inhibitors.

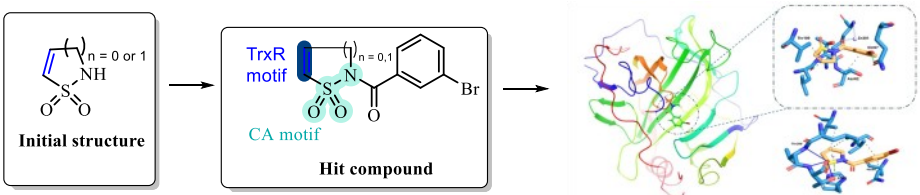
Development of potential dual TrxR and CA inhibitors

Aleksandrs Pustenko

The National Institute of Research and Innovation (NIRI)
aleksandrs.pustenko@niri.lv

The outlook remains challenging, as cancer – an aggressive disease associated with high mortality rates persists. Global cancer statistics remain alarming, with a continuous increase in both new cancer cases and cancer-related deaths worldwide[1]. Conventional cancer treatment modalities include surgery, radiation therapy, and chemotherapy[2]. An advanced and innovative approach in cancer treatment is the use of dual inhibitors[3]. Dual inhibitors are molecules that simultaneously target two enzymes, biological pathways, or molecular targets. The principal advantages of dual inhibitors include reduced tolerance development, minimization of potential adverse effects from drug–drug interactions, and reduced dose-limiting toxicities[3].The enzymes carbonic anhydrase (CA, EC 4.2.1.1) and thioredoxin reductase (TrxR, EC 1.8.1.9) have been identified as anticancer drug targets. Dual targeting of TrxR and cancer-associated CA isoforms (CA IX and CA XII) represents a promising anticancer strategy, as it simultaneously disrupts two essential cancer cell defense mechanisms: pH regulation, which is critical for cancer cell survival, and protection against oxidative stress[4].

We are working with sultam scaffolds as potential dual inhibitors of TrxR and cancer-associated CA isoforms (see Fig. 1).



hCA I/ II *Ki*, n=0;1 >100 μM
hCA IX Ki, n=0 (6.5); n=1 (6.7) μM
hCA XII Ki, n=0 (60); n=1 (15) μM
$TrxR_1$ IC_{50}, n=0 (180); n=1 (260) μM

Figure 1. Sultams as potential dual TrxR and CA inhibitors.

Acknowledgements
This study has been funded by the Recovery and Resilience Facility (RRF) grant No.41/OSI/PG (RRF project No.5.2.1.1.i.0/2/24/I/CFLA/001) and PostDoc Latvia project No.1.1.1.9/LZP/4/26/363.

References
1. Bray, F. et al. *CA Cancer J Clin*. **2024**, *74*, 229–263.
2. Liu, B.; Zhou, H.; Tan, L. et al. *Sig Transduct Target Ther*. **2024**, *9*, 175.
3. Roy, R. et al. *ACS Omega*, **2023,** *8*, 16532–16544.
4. Krasavin, M. et al. *J of Enzyme Inhib and Med Chem*, **2020**, *35*(1), 665–671.

Self-assembling styrylpyridinium and azo-analog fluorescent dyes in liposomal membrane models

Reinis Putralis[1,2], Karlis Pajuste[1], Nadiia Pikun[1], Ruslans Muhamadejevs[1], Mara Plotniece[2,3], Martins Rucins[1], Arkadij Sobolev[1], Aiva Plotniece[1,2]

[1] National Institute of Research and Innovation, Riga, Latvia
[2] Riga Stradiņš University, Faculty of Pharmacy, Riga, Latvia
[3] Faculty of Natural Sciences and Technology,
Riga Technical University, Riga, Latvia; aiva.plotniece@niri.lv

Styrylpyridinium (SP) derivatives are attractive fluorescent probes[1,2] and bioactive molecules with antimicrobial and antifungal activities[3]. The development of derivatives with improved photophysical performance remains an important research goal.

The aim of this work was *1*) to design and synthesize novel acceptor–π–donor *mono*- and *bis*-styrylpyridinium derivatives and their isosteric azo (N=N) *azo*-styryl-pyridinium analogues, *2*) to perform anion exchange, *3*) to study their photo-physical and self-assembly properties, interactions with liposomal membrane models.

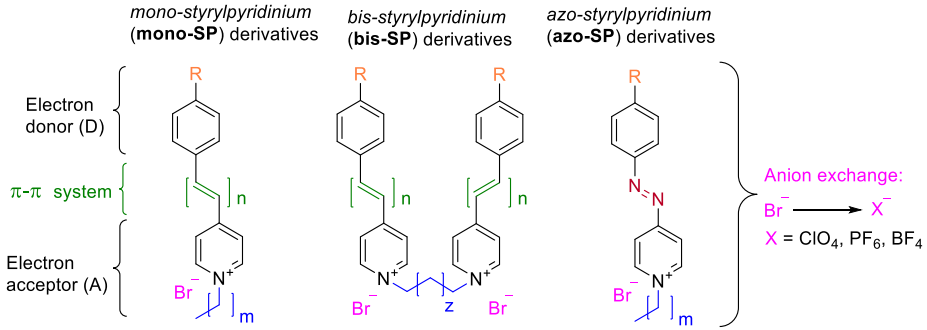


Figure 1. Structural diversification of SP dyes.

Novel SP derivatives with large Stokes shifts (>100 nm) and green emission were synthesized. Liposomal encapsulation enhanced fluorescence and increased Stokes shifts (>200 nm) for bis-SP derivatives. Bis-SP formed more ordered monolayers, while azo-SP derivatives altered monolayer properties upon light exposure.

Substituents and molecular structure strongly influence the physicochemical and photophysical properties of SP derivatives, supporting their putative application for development of fluorescent nanoprobes.

Acknowledgements
Funded by the Latvian Council of Science project lzp-2024/1-0364.

References
1. Zhang, C.; Yu, Z.; Liu, Y. et al. *RSC Adv* **2024**, *14*, 10255.
2. Gordel-Wójcik, M.; Nyk, M.; Bajorek, A. et al. *J Mol Liq* **2022**, *356*, 119007.
3. Vaitkienė, S.; Daugelavičius, R.; Sychrová, H. et al. *Front Microbiol* **2020**, *11*, 2077.

Beyond receptor affinity: biased multimodal signaling of HBK-15 in the search for rapid-acting antidepressant and procognitive strategies

Karolina Pytka[1], Angelika Jagielska[1,2], Kinga Sałaciak[1], Klaudia Lustyk[1], Monika Głuch-Lutwin[3], Barbara Mordyl[3], Bila Abdoul Fatahou Kabore[4], Séverine Morisset-Lopez[4]

[1] Laboratory of Experimental Neuropharmacology, Department of Pharmacodynamics, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna St, 30-688 Krakow, Poland
[2] Doctoral School of Medical and Health Sciences, Jagiellonian University Medical College, 16 Św. Łazarza St, 31-530 Krakow, Poland
[3] Department of Medicinal Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, 9 Medyczna St, 30-688 Krakow, Poland
[4] Centre de Biophysique Moléculaire, CNRS UPR 4301, Université d'Orléans, rue Charles Sadron, 45071 Orléans Cedex 2, France

Rapid-acting antidepressants are urgently needed, yet the discovery of new compounds is still often guided by receptor affinity rather than by an understanding of how individual signaling pathways translate into therapeutic-like effects. This is particularly important for multimodal ligands, whose pharmacological profile cannot be fully explained by binding to a single target.

HBK-15 is a multimodal compound with high affinity for serotonin 5-HT_{1A} and 5-HT_7 receptors, dopamine D_2/D_4 receptors, and sigma-1 receptors. What makes HBK-15 especially interesting from a drug discovery perspective is its pathway-selective signaling profile. At the 5-HT_{1A} receptor, HBK-15 preferentially promotes ERK1/2 phosphorylation, while showing no agonist activity in β-arrestin recruitment, cAMP signaling, or calcium mobilization assays. At the 5-HT_7 receptor, the compound also displays pathway-dependent activity, showing partial agonism in cAMP signaling without detectable β-arrestin recruitment. This functional selectivity suggests that HBK-15 may engage specific intracellular mechanisms rather than simply activating or blocking receptor targets in a uniform manner.

Acute administration of HBK-15 produces rapid antidepressant-like and procognitive effects in male mice, making it a useful model compound for exploring how pathway-selective and multimodal pharmacology may translate into behavioral outcomes. Current work focuses on molecular and cellular correlates of these effects, as well as potential sex-dependent differences in pharmacological activity. Particular attention is given to ERK1/2-related signaling as a potential molecular component of the broader multimodal pharmacological profile underlying the rapid behavioral effects of HBK-15.

By integrating receptor binding, pathway-selective signaling, and behavioral pharmacology, this talk will highlight HBK-15 as an example of how multimodal compounds can be evaluated beyond simple target affinity. This approach may help identify signaling signatures associated with rapid antidepressant-like and procognitive activity and guide the development of more mechanism-informed CNS drug discovery strategies.

Acknowledgements
This study was financially supported by the National Science Centre, Poland (grant numbers 2019/34/E/NZ7/00454, 2017/01/X/NZ7/00818, and 2024/53/B/NZ7/03768).

Use of a humanized *S. cerevisiae* expression system for the *in-vitro* selection of novel G-protein coupled receptor activating peptides

Ance Roga, Artis Linārs, Ivars Silamiķlis, Dita Gudrā, Linda Legzdiņa, Ramona Petrovska, Dāvids Fridmanis

National Institute of Research and Innovation, Riga, LV-1006, Latvia
ance.roga@niri.lv

G-protein-coupled receptors (GPCRs) constitute one of the largest families of mammalian membrane receptors and are high-value therapeutic targets. Despite their clinical significance, currently approved therapeutics target only ~10% of known GPCRs. Traditional peptide screening strategies, including mammalian cell assays and in silico predictions, are often limited by high experimental costs or low predictive accuracy. To address these challenges, we employed a humanized yeast *Saccharomyces cerevisiae* expression system for peptide discovery. In this platform, yeast survival and proliferation are strictly dependent on target GPCR activation. By co-expressing a target GPCR and a randomly generated peptide library in this system, natural selection drives preferential proliferation of yeast cells secreting receptor-activating peptides. Massively parallel next-generation sequencing is then used to track shifts in the random peptide pool over a 12-day culturing period, identifying enriched peptide coding sequences associated with cellular growth and receptor activation. This selection-guided culturing methodology offers a functional, high-throughput platform for identifying novel GPCR ligands. Ongoing optimizations in library generation and transformation protocols will further maximize the platform's utility, particularly for de-orphanizing highly selective peptide-binding receptors.

Dihydropyridine–arginine hybrids as promising candidates for glioblastoma treatment

Martins Rucins[1], Irene Rodriguez-Clemente[2,3], Karlis Pajuste[1], Arkadijs Sobolevs[1], Valentin Ceña[2,3], Aiva Plotniece[1]

[1] National Research and Innovation Institute, Riga, Latvia
[2]CIBER, Instituto de Salud Carlos III, Madrid, Spain
[3] Unidad Asociada Neurodeath, Facultad de Medicina, Universidad de Castilla-La Mancha, Albacete, Spain
martins.rucins@niri.lv

The project seeks to lay the groundwork for an innovative therapeutic strategy for glioblastoma. To achieve this, nanoparticles will be employed as delivery vehicles for both siRNA and an anticancer drug, enabling targeted treatment of the disease. The aim of the work: 1) design and synthesis of 1,4-dihydropyridine-arginine hybrid molecules (Fig. 1); 2) characterization of nanoparticles; 3) studies of biological activities; 4) evaluation of the structure-activity relationships.

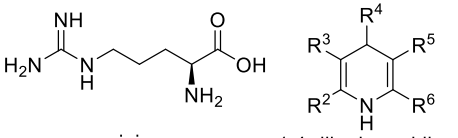


Figure 1. The hybrid molecules main fragments.

Natural amino acids and their derivatives offer significant advantages for biomedical and drug-delivery applications because of their low toxicity, biocompatibility, and chemical adaptability. The positively charged guanidinium group of protonated arginine enhances micelle–membrane interactions, thereby improving cellular internalization.[1] Several cationic 1,4-dihydropyridine (1,4-DHP) derivatives have been synthesized and shown to effectively deliver plasmid DNA into different cell lines *in vitro*. Initial studies revealed that double-charged 1,4-DHPs containing dodecyloxycarbonyl groups achieved particularly high levels of transfection efficiency.[2,3]

Original 1,4-DHP–arginine hybrid molecules with varying numbers and positions of arginine moieties were developed as nanoparticles for siRNA delivery to glioblastoma cells. Their siRNA binding, RNAse protection, and cytotoxicity were evaluated.

Acknowledgements
Work supported by the post-doctoral research grant 1.1.1.9/LZP/4/26/360 (M. Rucins) and LIOS internal grant IG-2026_19.

References
1. Zhao, Y.; Zhang, X.; Sun, M. et al. *Int. J. Biol. Macromol.* **2026**, 365, 152267.
2. Hyvönen, Z.; Plotniece, A.; Reine I. et al. *BBA*, **2000**, 1509, 451.
3. Pajuste, K.; Hyvönen, Z.; Petrichenko, O. et al. *New J Chem*. **2013**, 37, 3062.

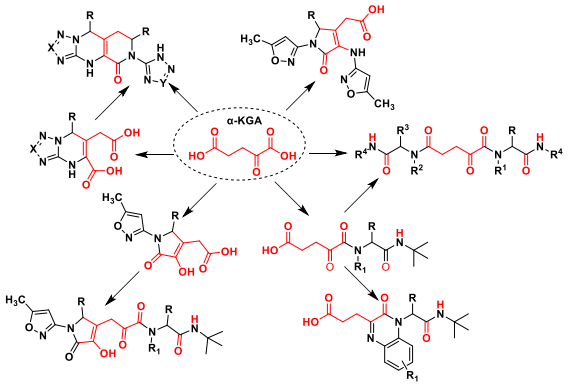
Multicomponent reactions involving α-ketoglutaric acid and transformations of their products

Y. I. Sakhno,[1] V. O. Honcharov,[1] V. A. Chebanov[1,2]

[1] Institute of Functional Materials Chemistry, SSI «Institute for Single Crystals» of NAS of Ukraine, Nauky Ave., 60, 61072, Kharkiv, Ukraine
[2] Education and Research Institute of Chemistry, V. N. Karazin Kharkiv National University, Svobody sq., 4, 61022, Kharkiv, Ukraine
yana.sakhno@gmail.com

Multicomponent reactions (MCRs) are efficient synthetic tools for preparing of structurally complex and multifunctional organic compounds with reduced resource consumption and waste generation compared to conventional stepwise syntheses.[1] Among the various building blocks used in multicomponent processes, α-ketoglutaric acid is a particularly attractive yet still insufficiently explored reagent and also plays an important role in many biochemical processes.[2]

The use of α-ketoglutaric acid in multicomponent transformations, including Doebner-type, Ugi, Ugi/aza-Wittig, Biginelli/Castagnoli-Cushman reactions, provides a convenient one-pot approach to structurally diverse and highly functionalized molecules (Scheme 1.). Combining these MCR strategies significantly increases molecular complexity and diversity while maintaining the advantages of operational simplicity and synthetic efficiency.[3,4]



Scheme 1. MCRs of α-Ketoglutaric acid and subsequent product transformations

The project of NRFU ‘Development of new materials based on supramolecular systems for biomedical and veterinary applications’ (2023.05/0003)

References

1. Mohlala, R. L.; Rashamuse, T. J.; Coyanis, E. M. *Frontiers in Chemistry.* **2024**, 12, 1469677.
2. Opsommer, L.-T. J. D. et al. *Chem. Soc. Rev.* **2025**, 54 (18), 8469–8523.
3. Sakhno, Y.; Radchenko, O.; Muravyova, E.; Sirko, S.; Shishkina, S.; Musatov, V.; Desenko, S.; Chebanov V. *Chem. Heterocycl. Compd.* **2021**, 57(3), 261–265.
4. Honcharov, V. O.; Sakhno, Y. I.; Shvets, O. H.; Saraev, V. E.; Shishkina, S. V; Shcherbakova, T. V; Chebanov, V. A. *Beilstein J. Org. Chem.* **2025**, 21, 2021–2029.

Design of furosemide amorphous solid dispersions: impact of excipient selection

K. Saršūns[1], N. Anspoka[1], R. Meija[2], R. Viter[3], V. Mohylyuk[4], A. Bērziņš[1]

[1] Department of Chemistry, Faculty of Medicine and Life Sciences, University of Latvia, Jelgavas 1, LV-1004, Riga, Latvia
[2] Institute of Chemical Physics, Faculty of Science and Technology, University of Latvia, Jelgavas 1, LV-1004, Riga, Latvia
[3] Institute of Atomic Physics and Spectroscopy, Faculty of Science and Technology, University of Latvia, Jelgavas 3, LV-1004, Riga, Latvia
[4] Leading Research Group, Faculty of Pharmacy, Riga Stradiņš University, Konsula 21, LV-1007, Riga, Latvia
kristaps.sarsuns@lu.lv

Amorphous solid dispersions (ASD) improve the solubility of poorly water-soluble active pharmaceutical ingredients (API) by stabilizing them in an amorphous polymer matrix. However, their thermodynamic instability can lead to recrystallization and reduced performance. Non-polymeric excipients, such as organic acids, sugars / sugar alcohols, and surfactants, can significantly influence ASD stability and dissolution through their effects on molecular interactions and mobility, but their roles remain difficult to predict.[1]

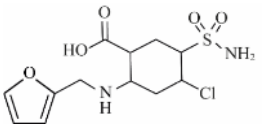


Figure 1. Molecular structure of furosemide.

This study examines ASD of furosemide (FSD), a poorly soluble loop diuretic, prepared with excipients from different functional classes. The amorphous nature was confirmed by XRPD, and morphology was analyzed by SEM. Intermolecular interactions were investigated using FTIR and Raman spectroscopy, while DSC was used to assess miscibility and phase behavior. Dissolution and supersaturation were evaluated by UV/Vis spectroscopy, and moisture effects were studied using dynamic vapor sorption.

Results show that excipient class strongly affects intermolecular interactions, dissolution performance, and moisture sensitivity, highlighting the importance of rational excipient selection in ASD design.

Acknowledgements
1.1.1.9 Research application No 1.1.1.9/LZP/2/25/213 of the Activity ”Post-doctoral Research” ”Enhancing *the physico-chemical stability and bioavailability of poorly water-soluble drugs using amorphous solid dispersions*”. The author thanks Latvian leading pharmaceutical manufacturer JSC “Olpha” for kindly providing a sample of furosemide.

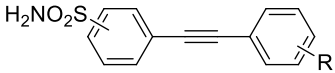
References
1. Zhang, X., Xing, H., Zhao, Y., Ma, Z. *Pharmaceutics*, **2018**, *10(3)*, 74.

3-/4-(Arylethynyl)benzenesulfonamide derivatives as promising inhibitors of tumor-associated hCA IX

Marjan Sobati[1], Raivis Žalubovskis[1], Claudiu T. Supuran[2]

[1] Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006 Riga, Latvia
[2] NEUROFARBA Department, Pharmaceutical and Nutraceutical Section, University of Florence, Via Ugo Schiff 6, 50019 Florence, Italy

A library of fourteen 3-/4-(arylethynyl)benzenesulfonamide derivatives were synthesized in up to 93% yield *via* Sonogashira coupling of 3-/4-bromobenzenesulfonamides with corresponding phenylacetylenes employing $Pd(PPh_3)_4/CuI/Et_3N$ combination as a catalytic system in refluxing THF (Fig. 1).[1] The inhibitory profiles of the synthesized compounds were evaluated against four different isoforms of human carbonic anhydrase (hCA I, II, IX and XII, EC 4.2.1.1).[2]



hCA I; K_i: 59.8-9612 nM
hCA II; K_i: 87.9-5820 nM
hCA IX; K_i: 1.1-408.7 nM
hCA XII; K_i: 2.3-410.2 nM

Figure 1. General structures of mesoionic compounds investigated in this study.

Analysis of the inhibition data revealed that approximately 85% of the compounds (12 of 14) exhibited weaker inhibition of the off-target isoform hCA I than AAZ, while all compounds were less potent against the second off-target isoform, hCA II, than the reference inhibitor. Conversely, all compounds displayed moderate to excellent inhibitory activity against hCA IX and hCA XII with affinity in the range of 1.1–408.7 nM and 2.3–410.2 nM, respectively. Among the tested compounds, the derivative bearing the sulfonamide group at the *meta* position and a *para*-methyl substituent on the terminal phenyl ring emerged as the most potent hCA IX inhibitor, exhibiting a K_i value of 1.1 nM, nearly 24-fold lower than that of AAZ. Moreover, this compound showed excellent selectivity for hCA IX, being 93-, 1554-, and 373-fold more selective over hCA I, hCA II, and hCA XII, respectively. Overall, these findings identify this class of compounds as a promising scaffold for the development of selective hCA IX inhibitors with potential anticancer applications.

References

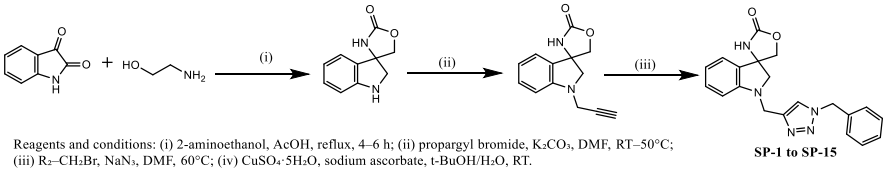
1. Chinchilla, R.; Najera, C. *Chem. Soc. Rev*. **2011**, *40*, 5084.
2. Sobati, M.; Abdoli, M.; Bonardi, A.; Gratteri, P.; Supuran, C.T.; Zalubovskis, R. *ACS Med. Chem. Lett*. **2023**, *14*, 1067.

Design, synthesis, and development of novel spiro-oxazolidinone–triazole hybrids as potential anti-infective agents against infertility-associated microbial pathogens

Bhavana Sriram, Manikandan Alagumuthu

Anti-Microbial Research Lab (AMRL), Dept. of Microbiology,
Saveetha Medical College and Hospital, SIMATS, Chennai-602105, India
mailtomicromani@gmail.com

Reproductive infections caused by microorganisms have been reported to be among the main factors responsible for infertility, whereas growing antibiotic resistance calls for the design of novel drugs. In the current study, 15 spiro-oxazolidinone-triazole hybrids (SP-1–SP-15) were designed and synthesized using a molecular hybridization approach and click chemistry through consecutive processes including spirocyclization, N-propargylation, and Cu(I)-catalyzed azide-alkyne cycloaddition reaction.



Reagents and conditions: (i) 2-aminoethanol, AcOH, reflux, 4–6 h; (ii) propargyl bromide, K_2CO_3, DMF, RT–50°C; (iii) R_2–CH_2Br, NaN_3, DMF, 60°C; (iv) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, t-BuOH/H_2O, RT.

Scheme 1. Synthetic route for the preparation of spiro-oxazolidinone–triazole hybrids (SP-1–SP-15).

Results from drug likeness and ADMET studies demonstrated excellent pharmacokinetic profiles, including good oral bioavailability, high gastrointestinal absorption, and minimal toxicity. Docking studies exhibited high binding affinity for the targets of interest, including infertility microbes. Compound SP-12 showed the highest activity had a docking score of –10.8 kcal/mol, and this was further confirmed via 100 ns molecular dynamics and MM/PBSA binding energy studies (–63.9 kcal/mol).

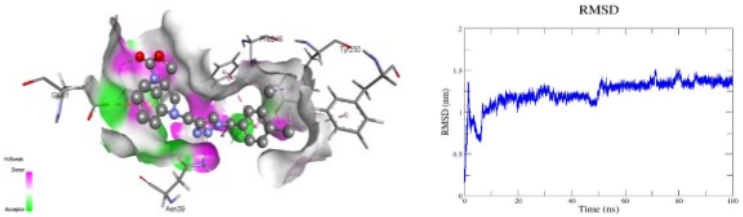


Figure 1. Molecular interaction of **SP-12** to *Trichomonas vaginalis* riboside hydrolase (PDB ID: 8OI7) and MD simulation RMSD of the docked complex.

In terms of antimicrobial efficacy testing, it was seen to be very effective against infertility-associated bacteria and had MIC values ranging from 0.06 to 0.78 µg/mL. Furthermore, it was also seen that the lead compounds could effectively inhibit the formation of biofilms by 82–91% and the formation of EPS by 65–74%. It was found via the cytotoxicity experiments that the IC_{50} values were more than 120 µM, resulting in SI >100.

References

1. WHO Bacterial Priority Pathogens List, 2024: Bacterial Pathogens of Public Health Importance to Guide Research, Development and Strategies to Prevent and Control Antimicrobial Resistance; World Health Organization: Geneva, Switzerland, 2024.
2. Jain, A.; Singh, K.; Das, D.; Singh, R. *Eur. J. Med. Chem.* 2023, *257*, 115506.
3. Kolodkin-Gal, I.; Cao, S.; Chai, L.; Böttcher, T.; Kolter, R.; Clardy, J.; Losick, R. *Science* 2012, *328*, 627–629.

Freedom Space 5.0: synthon-modular navigation of a 296-billion-compound synthetically accessible space for fragment growing and hit-to-lead optimisation

Olga Tarkhanova[1], Rita Gaidar[1], Anna Kapeliukha[1,3], Serhii Hlotov[1,3], Maryna Vasylchuk[1], Dmytro Radchenko[2], Yurii Moroz[2,3]

[1] Chemspace LLC, 85 Winston Churchill Street, Kyiv 02094, Ukraine
[2] Enamine Ltd, 78 Winston Churchill Street, Kyiv 02094, Ukraine
[3] Taras Shevchenko National University of Kyiv, 64/13 Volodymyrska Str., Kyiv 01601, Ukraine

Converting confirmed fragment or screening hits into synthetically accessible leads remains a central bottleneck in early drug discovery: chemistry that looks attractive on screen is often slow, expensive, or impossible to make. Freedom Space 5.0 addresses this at the design stage. It is a combinatorial chemical space of approximately 296 billion make-on-demand molecules, fully searchable through the Chemspace online platform using proprietary retrosynthetic algorithms that return only compounds with validated synthetic routes.

Freedom Space 5.0 is built for synthetic reliability rather than raw size: machine-learning classifiers trained on Enamine reaction-outcome data pre-select compatible building-block–synthon pairs before enumeration, giving an observed synthesis success rate above 80%. Around 215,000 commercially available building blocks are combined through 39 validated reaction protocols under drug- and lead-like physicochemical filters, with a dedicated synthon format keeping overlap with Enamine REAL Space close to zero. The same Chemspace platform also provides retrosynthetic access to Enamine's trillion-scale xREAL Space when broader coverage is required.

The platform's synthon modularity translates directly into a fragment-growing strategy. Because every compound is defined as a combination of synthons joined by validated reactions, the synthon carrying a confirmed binding motif can be anchored while the remaining positions are varied systematically — enumerating diverse yet synthetically feasible analogues around any validated fragment, each with a known synthetic route. We applied this workflow to the discovery of novel JAK1 inhibitors. An initial virtual screen of a 200-million-compound Freedom Space subset, followed by an ADP-Glo™ kinase assay, gave 9 confirmed hits, which were grouped into two classes by binding mode. For each hit, a retrosynthetic search across Freedom Space on the Chemspace platform resolved the constituent synthons; the hinge-binding synthon was then held constant to preserve the key kinase interaction, while the remaining moiety was varied to expand structural diversity without sacrificing synthetic accessibility. Biological evaluation of the resulting analogues confirmed the approach: 35 of 49 compounds showed >30% JAK1 inhibition at 20 μM, and potency profiling identified five submicromolar inhibitors (IC_{50} 0.24–0.81 μM). The campaign was run on an earlier Freedom Space generation; the synthon-modular principle is generation-independent and now operates at 296-billion scale in 5.0.

Coupling an ultra-large, synthetically validated space with retrosynthetic navigation turns hit expansion into a fast, orderable route from confirmed fragment to lead-like chemical matter — available on demand through a single platform.

Repurposing a fluorogenic screening strategy for the discovery of *C. difficile* cell-wall inhibitors

Sjoerd van der Gun[1], Sara Ait-Ikene[2], Patriks Eliass Grunsbergs[1], Raitis Bobrovs,[1] Aigars Jirgensons[1], Juan A. Hermoso[2]

[1] National Institute of Research and Innovation, Riga LV-1006, Latvia
[2] Instituto Química Física Blas Cabrera. CSIC. Madrid, Spain
aigars.jirgensons@niri.lv

L'D-Transpeptidases (ldt's) are cell wall constructing proteins in gram-positive bacteria. *C.difficile's* cell wall is for 75% constructed by ldt's[1], which makes it resistant to classic β-lactam antibiotics. This makes the species a good model organism for inhibitors against ldt's. Recent work uncovered 2 new ldt's bringing the total known in this species to 5, furthermore they discovered that 3 ldt's are critical for survivability in the species *C.difficile*[1]. It was found that these existed across two different protein domains conferring the same function while having differing architecture. Since the structures of these proteins have not been solved yet, ligands against ldt's are needed for co-crystallization in order to assist drug design and the wider investigation into bacterial cell wall construction.

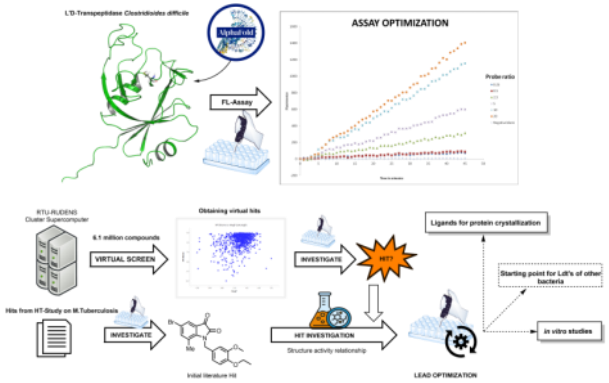


Figure 1. Process of drug discovery against L'D-Transpeptidases of *C. difficile*.

In this work we employ a fluorogenic assay and high throughput virtual screening to search for novel drug candidates against *C.difficile* across two distinct domain architectures. For this we synthetically enumerate one of the previously published[2] hits against *M.tuberculosis* and employ the same method to investigate inhibitors of ldt's.

Acknowledgements
This work was funded by the European Union under HORIZON-MSCA-2022-DN Cell Envelope Antibacterials (CLEAR), No 101119534.

References
1. K. W. Bollinger, U. Müh, K. L. Ocius, A. J. Apostolos, M. M. Pires, R. F. Helm, D. L. Popham, D. S. Weiss and C. D. Ellermeier, *Proc. Natl. Acad. Sci.*, **2024**, 121, e2408540121.
2. M. De Munnik, P. A. Lang, F. De Dios Anton, M. Cacho, R. H. Bates, J. Brem, B. Rodríguez Miquel and C. J. Schofield, *Chem. Sci.*, 2023, **14**, 7262–7278.

An antimicrobial screening pipeline for anti-Klebsiella natural products within the Gr-ADI consortium

Giel Vanreppelen[1,2], **Joleen Masschelein**[1,2]

[1] Laboratory for Biomolecular Discovery and Engineering, Department of Biology, KU Leuven, 3001 Leuven, Belgium
[2] VIB Center for Microbiology, VIB, 3001 Leuven, Belgium
giel.vanreppelen@kuleuven.be

Multidrug-resistant *Klebsiella pneumoniae* is a WHO priority pathogen for which the antibiotic discovery pipeline remains critically thin. Gr-ADI ("The Gram-Negative Antibiotic Discovery Innovator") is a multi-institutional consortium, funded by the Novo Nordisk Foundation, the Gates Foundation, and the Wellcome Trust. Our project consists of VIB/KU Leuven (coordinator) together with UCSD, DTU, Leiden University, NIOO-KNAW, TNO, Fundación MEDINA, and the Joint Genome Institute. The consortium aims to identify and develop novel natural product antibiotics active against this pathogen by combining ecology-inspired microbial elicitation, metabolomics and genome mining to link natural products to their biosynthetic origins, and structural characterization together with preclinical profiling of promising candidates.

Here we present the discovery pipeline being established at VIB/KU Leuven, which screens a pooled, dereplicated soil bacterial collection for anti-*Klebsiella* activity. A dual-arm pilot screen combines a solid-media assay, in which candidate strains are grown on agar and challenged with a *K. pneumoniae* soft-agar overlay to detect zones of growth inhibition, with a liquid-culture supernatant assay performed under OSMAC-style, medium-agnostic production conditions to capture secreted, diffusible activity. This will be complemented by elicitor screening, using co-cultivation and small-molecule elicitors to trigger the expression of otherwise silent biosynthetic gene clusters.

Although screening is at an early stage, we report initial proof-of-concept results, including reproducible zones of inhibition against *K. pneumoniae* from soil isolates. These preliminary findings demonstrate that the pipeline detects anti-*Klebsiella* activity and establish a foundation for scale-up, hit validation, and eventual hit-to-lead progression within the broader Gr-ADI consortium effort.

SinGel project stage I: synthesis of novel phenolic acid-antibiotic conjugates with enhanced antibacterial efficacy against causative agents of osteomyelitis

Una Lote Vītoliņa[1,2], Ance Bārzdiņa[2,3], Jurģis Krūmiņš[1,2], Renāte Teterovska[2,3], Agnese Brangule[2,3], Laura Krasnova[1], Karlis Pajuste[1], Arkadijs Sobolevs[1], Aiva Plotniece[1,2], Dace Bandere[2,3]

[1] National Institute of Research and Innovation, Riga, Latvia
[2] Department of Applied Pharmacy, Riga Stradins University, Riga, Latvia
[3] Baltic Biomaterials Centre of Excellence, Headquarters at Riga Technical University, Riga, Latvia

The presence of biofilms, antibacterial resistance, and intracellular infection aspects severely limits the current treatment efficacy of osteomyelitis[1]. The SinGel project aims to develop a thermosensitive, injectable, dually-loaded PLGA nanocarrier and free antibiotic (AB)-co-loaded hydrogel drug delivery system for a synergic and targeted treatment of osteomyelitis. We hypothesize that phenolic acids (PA), as strong antioxidants, could minimize the side effects of treatment while simultaneously enhancing the antibacterial and antibiofilm properties of antibiotics, such as meropenem and ciprofloxacin. The chemical structures of selected ABs and PAs are presented in Figure 1.

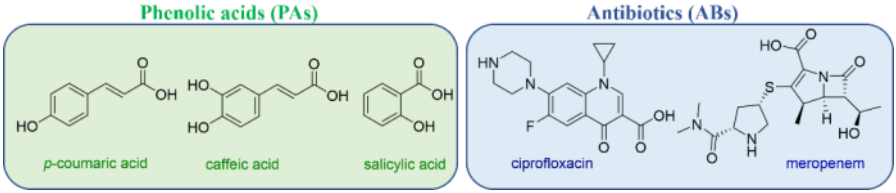


Figure 1. Structures of selected phenolic acids and antibiotics for conjugate synthesis.

Sensitivity and antibiofilm testing against 10 bacterial strains revealed that out of 9 PA tested, *p*-coumaric acid, caffeic acid, and salicylic acid showed the most promise as antibacterial agents.[2] Additionally, PAs can induce metabolic and morphological changes (e.g., membrane damage and filamentation) in bacteria.[2] Stronger biofilm biomass reduction effects against Gram-positive than Gram-negative strains were observed.[2] Synthetic pathways for the preparation of AB–PA conjugates will be discussed.

Acknowledgements
Funded by the Latvian Council of Science project No lzp-2025/1-0108 “Smart injectable nanoparticle-loaded hydrogel for synergic and targeted treatment of osteomyelitis (SinGel)”.

References
1. Lew, D.P. et al. *Lancet* **2004**, *364*, 369–379.
2. Bārzdiņa, A. et al. *Microbiol. Spectr*. **2026**, accepted for publication

Heteroaromatic aminophosphonates as selective nanomolar inhibitors of carbonic anhydrases IX and XII

Manuela Voráčová,[1] Elena Andreucci,[2] Alessio Biagioni,[2] Lucia Magnelli,[2] Marija Skvorcova,[1,3] Paavali Metso,[1] Ashenafi Legehar,[1] Martina Panerai,[4] Henri Xhaard,[1] Andrea Angeli,[4] Fabrizio Carta,[4] Paula Kiuru[1]

[1] Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Viikinkaari 5, 00790, Helsinki, Finland
[2] Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Viale Morgagni 50, 50134, Florence, Italy
[3] National Institute of Research and Innovation, Aizkraukles 21, LV-1006, Riga, Latvia
[4] NEUROFARBA Department, Pharmaceutical and Nutraceutical section University of Florence, via Ugo Schiff 6, 50019, Sesto Fiorentino, Italy

Cancer adapts through various mechanisms to support growth, survival, and metastasis, with the tumor microenvironment playing a key role. Hypoxia and acidic conditions promote tumor progression, immune evasion, and therapy resistance.[1] Human carbonic anhydrase IX (hCA IX) and XII (hCA XII), upregulated in hypoxic tumors via HIF-1α, regulate pH balance and support cancer cell survival. Their selective expression in tumors makes them promising targets for anticancer therapy, and their inhibition shows potential to impair tumor growth and enhance current treatments.[2]

We synthesized 48 heteroaromatic aminophosphonates, including 18 water-soluble derivatives.[3] Enzymatic assays showed strong selectivity for tumor-associated carbonic anhydrases hCA IX and hCA XII. The most potent compound displayed nanomolar inhibition (K_i = 34.8 nM for hCA IX; 21.4 nM for hCA XII) with minimal off-target activity (>1000× selectivity).

Cytotoxicity in hCA IX–expressing cancer cell lines (melanoma, colon, and breast), as well as in normal cells (HUVEC and HFE-145), will be discussed alongside structure–activity relationships and the role of the phosphorus moiety in inhibition, as determined by molecular modeling.

References

1. Chen, Z.; Han, F.; Du, Y.; Shi, H.; Zhou, W. *Signal Transduct. Target. Ther*. **2023**, *8*, 70.
2. Nerella, S.G.; Thacker, P.S.; Arifuddin, M.; Supuran, C.T. *Eur. J. Med. Chem. Rep.* **2024**, *10*, 100131.
3. Voráčová, M.; Andreucci, E.; Biagioni, A.; Magnelli, L.; Skvorcova, M.; Legehar, A; Xhaard, H; Carta, F.; Kiuru P. *Under review*.