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2nd Conference on Innovative Chemistry and Chemical Biology

1st and 2nd October 2026, Olomouc, Czech Republic

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2nd Conference on Innovative Chemistry and Chemical Biology

Thursday 1.10.		
8:30 – 9:30	REGISTRATION	
CHAIR: Alexander Dömling		
9:30 – 9:45	Alexander Dömling	Opening speech
9:45 – 9:55	Pavel Banáš	Introductory speech
9:55 – 10:35	Bernhard Westermann	Phytoceramides – Scaffold Diversification and Applications as Adjuvants
10:35 – 10:55	Imma Capriello	From Droplets to Staples: Echo-Enabled Ugi-4CR Peptide Stapling for Targeting p53–MDM2
10:55 – 11:15	Elisabetta La Scola	From Modular synthesis to systematic interrogation of triazolopiperazine reaction space
11:15 – 11:55	Matthew Groves	Allosteric Inhibition in Aspartate Transcarbamylase: Applications from malaria to herbicides
11:55 – 12:55	LUNCH	
	CHAIR: Bernhard Westermann	
13:05 – 13:45	Petr Džubák	Reading a compound's mechanism of action with Cell Painting
13:45 – 14:05	Emis Ingenito	Automated nanolitre chemistry for direct-to-biology IL-17A hit discovery
14:05 – 14:25	Kaoud Salama	One Reaction, Multiple Rings: Automated Discovery of Ring-Divergent Ugi Chemistry
14:25 – 15:05	Shabnam Shaabani	Drug Discovery Acceleration by Automated Chemistry and Direct to Biology
15:05 – 15:35	COFFEE BREAK	
	CHAIR: Jacek Plewka	
15:35 – 16:15	Katarzyna Magiera-Mularz	Beyond binding: structural biology and NMR insights into protein modulation
16:15 – 16:35	Foteini Kakari	C-N Atropisomerism: Built by MCRs
16:35 – 17:15	Philip Elsinga	Challenges in synthesis of ¹⁸ F-tracers for Positron Emission Tomography
17:15 – 17:35	Maria-Aikaterini Giannakaki	A Telescoped One-pot Strategy for Functionalized Fused Heterocycles
17:40	END OF THE 1 ST DAY	

Friday 2.10.

CHAIR: Dinos Neochoritis

9:00 – 9:40	Andreas Brunschweiler	Synthesis and screening of DNA-encoded macrocycle libraries
9:40 – 10:00	Vishwanatha Thimmalapura Marulappa	One-Pot Installation of Backbone-Embedded Pyrazoles in Peptides and its application to bioconjugation
10:00 – 10:20	Riccardo Fusco	Reading a reaction space: quantum-chemical descriptors and machine learning for a triazolopiperazine library
10:20 – 11:00	Tryfon Zarganis-Tzitzikas	Developing GAL3 Degraders for the Treatment of Alzheimer’s Disease
11:00 – 11:20	Mayur Mukim	From Reaction Discovery to Reaction Grammar: A Topology-Generating Split-Interrupted Oxo-Carboxylic Acid Multicomponent Reaction
11:20 – 12:20	LUNCH	
CHAIR: Katarzyna Magiera-Mularz		
12:20 – 13:00	Jacek Plewka	Small Molecule LAG-3 Inhibitors Synergize with Anti-PD-L1 Therapy in Cancer Immunotherapy
13:00 – 13:20	Samatha Masineni	Multicomponent Reaction-Based Synthesis and Anticancer Screening of Novel Benzo[f]tetrazolo[1,5-a][1,4]diazepines
13:20 – 13:40	Thiago Moreira Pereira	Development of TMP-0193: A novel modulator of cardiac diastolic function
13:40 – 14:20	Dinos Neochoritis	MCRs: Unlocking Chemical Space From Molecular Diversity to Function and New Modalities
14:20	END OF THE CONFERENCE	

Alexander Dömling

ERA Chair, Innovative chemistry Group, Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry and Czech Advanced Technology and Research Institute, Palacký University in Olomouc, Olomouc, Czech Republic

Short biography: Prof. Dr. Alexander Dömling is ERA Chair of Innovative Chemistry at Palacký University Olomouc, Czech Republic. He obtained his Ph.D. under Prof. Ivar Ugi at the Technical University of Munich and carried out postdoctoral research with Nobel Laureate Prof. Barry Sharpless at The Scripps Research Institute. He subsequently held a professorship at the University of Pittsburgh and, from 2011, served as Chair of Drug Design at the University of Groningen, where he established and led a multidisciplinary drug-design research program and previously served as Chair of Drug Design at the University of Groningen. Prof. Dömling has extensive experience in translating academic research into biotechnology, having founded or co-founded several biotech companies, including Morphochem, Telesis, SMIO, and Carmolex, and has contributed to the development of innovative technologies for drug discovery. His research combines multicomponent reactions, novel chemical modalities, high-throughput and automated synthesis, and structure-based drug design.

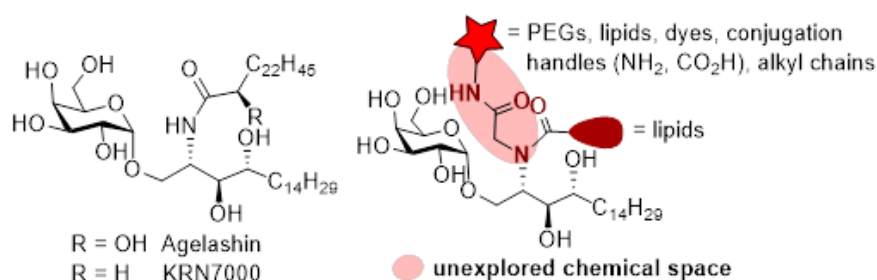


Phytoceramides – Scaffold Diversification and Applications as Adjuvants

Bernhard Westermann

Leibniz-Institute of Plant Biochemistry, Department of Bioorganic Chemistry, Weinberg 3, 06120 Halle, Germany

Adjuvants are necessary requirements for improving the performance of vaccines. α -Galactosylceramides (α -GalCer, e.g. KRN7000) have attracted particular interest due to their ability to activate iNKT cells and B cell activation. Although the structure of this glycolipid, which originates from the marine natural product Agelasphin, has been extensively studied and modified to broaden its adjuvant properties, the modifications seem to be rather limited. This restricts the potential discovery of new applications. Here, we present the use of multicomponent reactions to extend the chemical space of glycolipids beyond the classical modifications. For the first time, we show that the amide linkage is a suitable diversification point for the introduction of a variety of moieties that allow the modulation of adjuvant properties. We will also present diversifications of proteins by multi-component reactions, which may be considered as bioconjugate ligation methods.



A. R. Humpierre et al. *Bioconjugate Chem.* **2020**, 31, 2231 – 2240.

(10.1021/acs.bioconjchem.0c00423)

Y. Mendez et al. *ACS omega* **2020**, 5, 25505 – 25510 (10.1021/acsomega.0c03728)

Y. Mendez et al. *ACIE* **2024**, 63, e202310983 (10.1002/anie.202310983)

A. R. Humpierre et al. *Commun. Chem.* **2026**; 9:46 (10.1038/s42004-025-01827-1)

Short biography: Prof. Dr. Bernhard Westermann is Group Leader of Biofunctional Synthesis at the Leibniz Institute of Plant Biochemistry (IPB), Halle, Germany, and Professor at Martin Luther University Halle-Wittenberg. He received his Ph.D. from the University of Paderborn in 1989 and carried out postdoctoral research at the University of Toronto, Canada. His research focuses on natural product chemistry, bioactive molecules, multicomponent reactions, diversity-oriented synthesis, and sustainable chemistry, with particular emphasis on developing innovative synthetic approaches for biologically relevant compounds. He has published more than 120 scientific papers and holds several patents.



From Droplets to Staples: Echo-Enabled Ugi-4CR Peptide Stapling for Targeting p53–MDM2

Imma Capriello^{1,2} Vishwanatha Thimmalapura Marulappa,^{1,2} Katarzyna Magiera-Mularz,³ Jacek Plewka,³ and Alexander Dömling^{1,2}

¹*Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic*

²*Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic*

³*Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, Krakow, 30-387, Poland*

Peptide stapling is a promising strategy for targeting protein–protein interactions, but the development of effective stapled peptides requires multifactorial optimization of solubility, stability, cellular penetration, target activity, and potentially oral bioavailability. Conventional stapled-peptide discovery, however, often relies on sequential, time-consuming, and resource-intensive synthesis, limiting the chemical space that can be efficiently explored.

In this work, we investigate the Ugi four-component reaction (Ugi-4CR) as a modular approach to staple p53-derived peptides targeting MDM2 through appropriately positioned lysine and aspartic/glutamic acid residues. Variation of the carbonyl and isocyanide components enables staple formation and chemical diversification in a single multicomponent reaction, providing rapid access to structurally diverse analogues.

To accelerate this process, we developed a 384-well Echo-enabled workflow that miniaturizes Ugi-4CR peptide stapling to the nanomole scale, enabling hundreds of novel stapled-peptide derivatives to be synthesized and analyzed within just a few hours. Reaction outcomes are assessed using LC–MS and Echo MS, while NMR binding studies are used to evaluate interaction with MDM2.

This approach integrates multicomponent chemistry, acoustic liquid handling, and rapid mass-spectrometric analysis into a highly parallel and material-efficient platform for stapled-peptide discovery and optimization.

From modular synthesis to systematic interrogation of triazolopiperzine reaction space

Elisabetta La Scola,^{a,b} Samatha Masineni,^{a,b} Riccardo Fusco,^{a,b} Alexander Dömling^{*a,b}

^a*Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacky University Olomouc, Slechtitelu 27, Olomouc, 783 71, Czech Republic*

^b*Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University and University Hospital Olomouc, Olomouc, Czech Republic*

Triazolopiperazines are medicinally relevant scaffolds represented in clinically important compounds such as Sitagliptin and Fezolinetant^{1,2}, as well as in other biologically active series including P2X7 antagonists, antimalarial compounds and antibacterial agents. Their compact, nitrogen-rich architecture combines a polar heteroaromatic motif with a saturated ring that defines three-dimensional exit vectors and provides multiple opportunities for analogue diversification. This combination of polarity, three-dimensionality and structural tunability makes the scaffold particularly attractive for medicinal chemistry, but current synthetic routes are poorly suited to systematic analogue exploration.

Here, we developed a modular one-pot, two-stage synthesis that provides direct access to diversified triazolopiperazines and is compatible with miniaturized high-throughput experimentation. The synthetic utility of the approach was demonstrated through expanded substrate scope and downstream functionalization.

To move from reaction development to a systematic assessment of its broader applicability, we then investigated both condition and chemical space using high-throughput experimentation. Acoustic droplet ejection provided a common miniaturized experimental framework for both stages, enabling flexible reaction-matrix assembly from shared reagent source plates at nanoliter scale. A sequential design of experiments strategy was first used to investigate and refine the reaction conditions, followed by a 1,536-reaction campaign to explore chemical space across diverse building block combinations. High-throughput analytical processing transformed the reaction campaign into a consistent, structured dataset suitable for subsequent structure-reactivity analysis.

Overall, this work turns triazolopiperazine synthesis from a route to individual targets into a framework for systematically generating, mapping and learning from analogue space.

References

1. Kim, D.; Kowalchick, J. E.; Brockunier, L. L.; Parmee, E. R.; Eiermann, G. J.; Fisher, M. H.; He, H.; Leiting, B.; Lyons, K.; Scapin, G.; et al. Discovery of Potent and Selective Dipeptidyl Peptidase IV Inhibitors Derived from β -Aminoamides Bearing Substituted Triazolopiperazines. *J. Med. Chem.* 2008, 51, 589–602. <https://doi.org/10.1021/jm070330v>

Allosteric Inhibition in Aspartate Transcarbamylase: Applications from malaria to herbicides

Matthew Groves

School of Pharmacy, University of Groningen, The Netherlands

Pyrimidine biosynthesis is an essential function in all living cells and is supported by two distinct pathways: de novo synthesis and salvage. Different cell types are more dependent upon different pathways, but generally rapidly dividing cells are dependent on de novo synthesis. Aspartate transcarbamylase catalyses the first committed reaction in this pathway and is therefore an attractive drug target for multiple systems. However, the current ATCase gold standard inhibitor is a transition state mimic and has limited selectivity between human and pathogens. In this talk, I will describe the discovery of a new allosteric inhibitor of ATCase and its potential in multiple disease systems and as a herbicide.

Short biography: Dr. Matthew Groves is an Assistant Professor at the Groningen Research Institute of Pharmacy, University of Groningen, Netherlands. He obtained his Ph.D. under Prof. Sir Tom Blundell and subsequently conducted postdoctoral research at Oxford and Heidelberg. He has extensive experience in structural biology, protein crystallography, molecular biophysics, and X-ray crystallography, with a particular focus on understanding protein structure and function.



Reading a compound's mechanism of action with Cell Painting

MUDr. Petr Džubák

Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic

Finding a bioactive compound is rarely the bottleneck; explaining it is. What does the molecule do inside a cell, and through which pathway or protein? High-throughput screening, including screens in engineered reporter cell lines, delivers hits at scale but says little about how they act. Cell Painting, an unbiased high-content assay, closes this gap by recording the morphological fingerprint a compound leaves across cellular organelles. Hits can then be grouped by mode of action and matched against annotated reference sets such as the EU-OPENSOURCE Bioactives. In a senolytic screen, this approach placed MCOPPB, its derivative MS1108 and several other hits in one cluster with known autophagy inhibitors, including bafilomycin A1 and chloroquine. Follow-up experiments confirmed that these compounds eliminate senescent cells by disrupting autophagic flux. Autophagy thus emerges as a survival dependency of senescent cells, and its inhibitors as a mechanistically distinct class of senolytics. Machine-learning analysis of the images makes such profiles predictive of bioactivity and toxicity, giving chemists an early, target-agnostic readout of which scaffolds deserve the next round of synthesis.



Automated nanolitre chemistry for direct-to-biology IL-17A hit discovery

Emis Ingenito^{a,b}, Sufyan Iqbal^{a,b}, Jacek Plewka^c, Alexander Dömling^{a,b}

^aRegional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic.

^bInstitute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic.

^cFaculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387 Krakow, Poland.

Interleukin-17A (IL-17A) is a key pro-inflammatory cytokine involved in several autoimmune and inflammatory diseases.¹ Although IL-17A is already a clinically validated target for antibody-based therapies, the discovery of small-molecule ligands remains challenging because of its large and relatively flat protein-protein interaction interface.² This creates a need for faster and more efficient approaches to explore new small molecules chemical space around this target.

Here, we developed an automated nanolitre-scale workflow combining chemical synthesis, analytical characterization and direct biological screening for the discovery of small molecules targeting IL-17A. A library of bisamide-containing compounds was generated using the ammonia-based Ugi four-component reaction, which provides rapid access to molecular scaffolds containing pharmacophoric features known to interact with the IL-17A dimer interface. Library synthesis was miniaturized using Echo[®] acoustic droplet ejection (ADE), allowing automated reaction setup at the nanolitre scale while reducing reagent and solvent consumption. Following synthesis, the library was first assessed by UPLC-MS and then directly tested in a single-dose Diantus-based IL-17A binding assay.

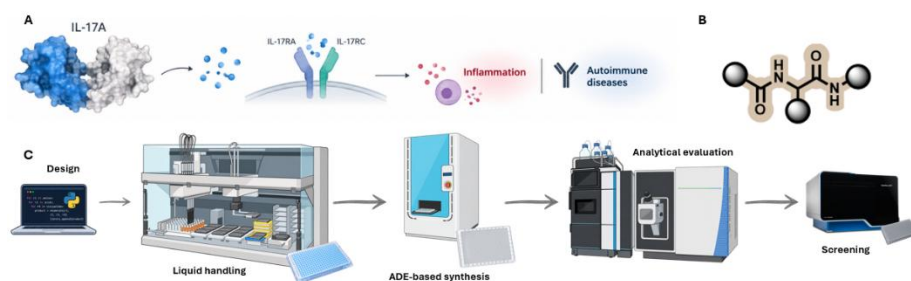


Figure 1. Overview of the IL-17A direct-to-biology workflow. (A) IL-17A signaling and disease relevance. (B) Bisamide structure. (C) Overview of the performed workflow.

This workflow allowed rapid progression from synthesis to biological screening and identified several compounds showing binding-compatible responses. These preliminary hits will be taken forward for resynthesis, full characterization and further biological validation. Overall, the study highlights the potential of combining ADE-based multicomponent chemistry with direct-to-biology screening for the rapid exploration of challenging protein–protein interaction targets.

References: Zhang B, Dömling A. Small molecule modulators of IL-17A/IL-17RA: a patent review (2013-2021). *Expert Opin Ther Pat.* 2022;32(11):1161-1173. doi:10.1080/13543776.2022.2143264.

One Reaction, Multiple Rings: Automated Discovery of Ring-Divergent Ugi Chemistry

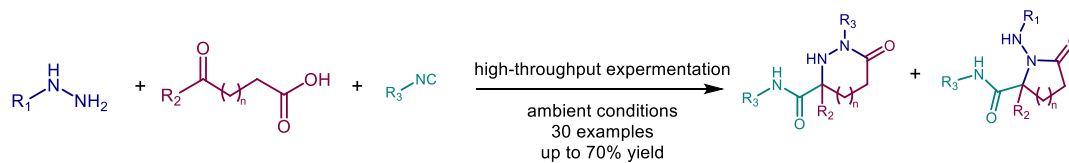
Kaoud Salama,^{1,2} Fiorella Meneghetti,³ Matteo Mori,³ Alexander Dömling^{1,2*}

¹Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic

²Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Hněvotínská 5, Olomouc, 779 00, Czech Republic.

³Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, XtaLab, Via L. Mangiagalli 25, 20133 Milano, Italy

The rapid generation of structurally diverse, medically relevant scaffolds remains a central challenge in modern synthetic and medicinal chemistry. Here, we report an automated, ultra-microscale platform for ring-divergent synthesis based on an Interrupted Ugi-4CR involving oxoacids, hydrazine derivatives, and isocyanides. The methodology enables divergent cyclization from a common set of building blocks, providing access to distinct ring systems in a single operation.



Reaction discovery was performed at a 50 nmol in 384-well plates. An Opentrons OT-2 was employed for stock-solution preparation, while Acoustic Dispensing (Echo) enabled precise nanoliter-scale assembly of reaction mixtures. An initial 384-reaction matrix comprising 16 oxoacids and 24 hydrazines mapped reactivity and ring divergence, followed by a second 384-reaction screen incorporating a diverse isocyanide set, achieving an approximately 100% reaction success rate. Reaction outcomes were rapidly assessed by High-throughput LC-MS. Representative reactions were subsequently translated to preparative scale, delivering 40–70% isolated yields, with structures validated by X-ray and NMR.

This workflow integrates multicomponent synthesis, automated experimentation, and rapid analytical feedback to accelerate access to ring-diverse chemical space and provides a general strategy for high-throughput scaffold discovery.

Drug Discovery Acceleration by Automated Chemistry and Direct-to-Biology

Shabnam Shaabani

Bayer Pharma, Berlin

Automation, miniaturization, and downscaling of synthetic chemistry not only accelerate the “make” phase of the Design-Make-Test-Analyze (DMTA) cycle but also improve the sustainability of chemical processes. The Direct-to-Biology (D2B) approach enables the testing of crude chemical reaction mixtures directly in biological assays, bypassing time-consuming purification steps. Combining automated and miniaturized synthesis with D2B and AI-driven design is an emerging field, currently experiencing a renaissance in the era of big data and artificial intelligence, enabling faster discovery of novel drug candidates. This integrated approach accelerates DMTA cycles and enhances environmental sustainability by increasing efficiency and reducing waste.

Details of our technology platform at the Automated Medicinal Chemistry (AMC) lab at Bayer Pharma in Berlin will be presented describing plate-based chemistry, automated purification, automated quantification, and a reformatting unit to enable the delivery of diverse libraries of test compounds - both purified and unpurified - in assay-ready plate formats. To better support portfolio projects, we continuously expand the accessible chemical reaction space, from Suzuki and Buchwald reactions to multi-step macrocycle derivatization.

Short biography: Dr. Shabnam Shaabani currently is leading Direct to Biology, Automated and Miniaturized Medicinal Chemistry efforts in Bayer Pharma, Berlin. Following her PhD training in organic chemistry, she joined the lab of Prof. Dömling at the University of Groningen. There she developed a platform for Miniaturization of Chemistry and Direct to Biology. In 2021, Dr Shaabani was awarded Alexander von Humboldt postdoctoral research fellowship to explore the RNA world and discover RNA binding small molecules at Technical University of Munich.



Beyond binding: structural biology and NMR insights into protein modulation

Katarzyna Magiera-Mularz,¹ Bogdan Musielak,¹ Katarzyna Golebiowska-Mendroch,¹, Alicja Borjal,^{1,2} Jacek Plewka¹

¹Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387, Krakow, Poland

²Jagiellonian University, Doctoral School of Exact and Natural Sciences, prof. S. Lojasiewicza 11, 30-348 Krakow, Poland

Understanding how small molecules influence protein function requires approaches that capture both molecular interactions and changes in protein behaviour. Structural methods provide information on ligand recognition and complex architecture, while NMR spectroscopy allows investigation of conformational changes, dynamics and interactions in solution.

This lecture will present examples illustrating how structural biology and NMR can be combined to characterize different modes of protein modulation by small molecules.¹⁻³ Studies on PD-L1 ligands will demonstrate how these approaches distinguish between compounds that induce protein oligomerization and those that modulate the target through alternative mechanisms.

The second part will focus on targeted protein degradation and the development of an NMR-based strategy to investigate PROTAC complexes. Since degrader activity depends on the formation and properties of multi-component protein assemblies, understanding their dynamics may provide additional mechanistic information beyond binding affinity alone.

The integration of structural, biophysical and cellular approaches offers a framework for connecting molecular mechanisms with functional outcomes in drug discovery.

References: Rodriguez I., (...), and Magiera-Mularz K.* (2023), Structural and biological characterization of pAC65, a macrocyclic peptide that blocks PD-L1 with equivalent potency to the FDA-approved antibodies. *Molecular Cancer*, 22, 150; DOI: 10.1186/s12943-023-01853-4; Magiera-Mularz K.*, et al. (2021), Human and mouse PD-L1: similar molecular structure, but different druggability profiles. *iScience*, 2021, 24, 101960; DOI: 10.1016/j.isci.2020.101960; W. Zou, et al (2026), Discovery of natural product-derived rosavin as a programmed death-ligand 1 inhibitor for cancer immunotherapy, *Phytomedicine*, 158609; DOI: 10.1016/j.phymed.2026.158609.

C-N Atropisomerism: Built by MCRs

Kakari Foteini, Giannakaki Maria Aikaterini and Neochoritis Konstantinos

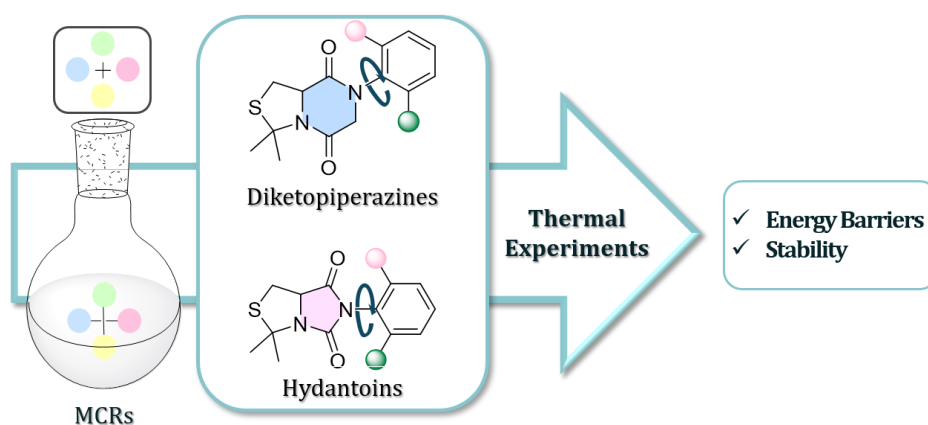
Department of Chemistry, University of Crete, Voutes, 70013, Heraklion, Greece

Keywords: *Atropisomers, Multicomponent Reactions, diketopiperazines, hydantoins, energy barrier*

The synthesis of chiral scaffolds represents a critical field in organic synthesis, as chirality decisively influences physicochemical properties and biological interactions with the targeted molecules. The present study focuses on the synthesis of novel chiral atropisomers, through a sequential multicomponent synthetic strategy, leveraging their unique structural properties and potential pharmacological applications.

The synthesis of these atropisomers was achieved via a union of multicomponent reactions (MCRs) in a one-pot approach. The mAUCy method (modified Asinger, Ugi and Cyclization), gave access to two extensive libraries of axially chiral compounds, consisting of thiazolo-1,5-hydantoins and thiazolo-2,5-diketopiperazines.

A primary objective was the investigation of the rotational energy barriers of these axially chiral molecules through systematic thermal experiments, which allowed their classification according to their configurational stability. The experimental thermal data were correlated with theoretical DFT calculations to evaluate the stability and the rotational behavior of the atropisomeric scaffolds.



References: [1] Dömling, A., et al, Chemistry and Biology of Multicomponent Reactions. Chemical Reviews 2012, 112 (6), 3083-3135. [2] Maria-Aikaterini Giannakaki, Marios Zingiridis, Konstantinos G. Froudas, and Constantinos G. Neochoritis, Organic Letters 2026 28 (6), 2096-2101.

Challenges in synthesis of ^{18}F -tracers for Positron Emission Tomography

Prof. Philip H. Elsinga

*University Medical Center Groningen, Department of Nuclear Medicine and Molecular Imaging,
Hanzeplein 1, 9713GZ Groningen, The Netherlands*

Positron Emission Tomography (PET) is a powerful molecular imaging modality that allows the non-invasive visualization and quantification of biological processes in living subjects through the use of radiolabelled compounds. Among the available radionuclides, fluorine-18 (^{18}F) is the most widely employed because of its favourable physical characteristics, including a half-life of approximately 110 minutes, a high positron emission yield, and the excellent image resolution it provides in PET studies. These properties have made ^{18}F the radionuclide of choice for both clinical and research applications. Despite the growing demand for novel PET tracers, their development remains a slow and resource-intensive process. Current workflows rely heavily on manual radiosynthesis, iterative optimization, and empirical decision-making, requiring substantial human expertise and intervention. Moreover, radiochemical research presents unique challenges, including the need to work safely with radioactive materials, the handling of minute quantities of radiolabelled compounds, and the strict time constraints imposed by radionuclide decay. A key factor determining the successful development of new PET tracers is the availability of robust radiolabelling methodologies. Ideally, an ^{18}F -label should be introduced at virtually any position within a biologically active molecule, enabling rapid exploration of new imaging agents. However, technical limitations in radiochemistry continue to restrict this flexibility, making the development of innovative labelling strategies a major priority and persistent bottleneck in the field.

Prof. Philip Elsinga will present recent advances from his research group aimed at accelerating PET tracer development, including chip-based radiochemistry, novel ^{18}F click-labelling approaches, react-and-release strategies that enable reuse of valuable precursor materials, and multiplex labelling technologies for more efficient tracer production and evaluation.

Short biography: Prof. Dr. Philip H. Elsinga is an organic chemist by training and he obtained his PhD in 1995 at the University of Groningen. He is involved in PET-related radiopharmaceutical research and translation of radiopharmaceuticals to the clinic. Main focus was firstly directed to PET-labelled amino acids, receptor ligands for the beta-adrenergic receptor and substrates for P-glycoprotein. Later on, his interest broadened to other PET-radiopharmaceuticals, such as ^{18}F -labelled peptides, receptor antagonists, bacterial infection tracers and artificial amino acids for neuroendocrine tumors. In 2011 Philip Elsinga was appointed as full professor PET-radiochemistry. He is author of >250 peer-reviewed articles. International activities are Editor-in-Chief of European Journal of Nuclear Medicine and Molecular Imaging Radiopharmacy and Chemistry and invited expert for IAEA.



A Telescoped One-pot Strategy for Functionalized Fused Heterocycles

Maria-Aikaterini Giannakaki, Marios Zingiridis, Constantinos G. Neochoritis

Department of Chemistry, University of Crete, Voutes, 70013, Heraklion, Greece

Keywords: *mAUCy*, *thiazolo-hydantoin*s, *thiazolo-diketopiperazine*s, *telescoped*, *Multicomponent reactions*

Rapid access to diverse heterocyclic scaffolds is essential for advancing synthetic organic methodology. This work describes a novel three-layer transformation, the modified Asinger-Ugi-Cyclization (*mAUCy*), which leverages multicomponent reaction (MCR) chemistry to construct complex thiazolo-hydantoin and diketopiperazines (DKPs).

Operationally, the methodology is streamlined into a telescoped one-pot sequence requiring no intermediate isolation, furnishing target heterocycles in under three hours. High atom economy, exceptional operational simplicity, and seamless scalability highlight its utility for sustainable synthesis. Furthermore, the platform introduces flexible functional handles that facilitate late-stage modification, establishing the *mAUCy* strategy as a practical engine for generating diverse libraries of biologically active compounds.

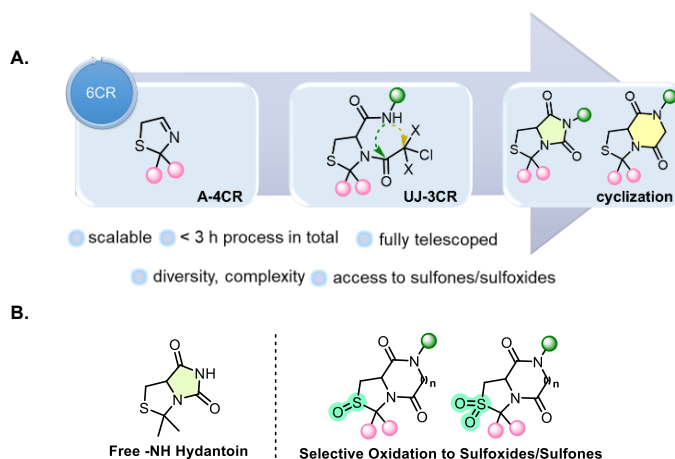


Figure 1. (A) The *mAUCy* Strategy, (B) Late-stage functionalization

References: Giannakaki M.A., Zingiridis M., Froudas K. G., Neochoritis C. G., (2026). A Three-Layer Transformation Strategy toward Functionalized Fused Hydantoins and Diketopiperazines. *Organic Letters*, 28(6), 2096-2101.

Synthesis and screening of DNA-encoded macrocycle libraries

Prof. Andreas Brunschweiler

Chair of Pharmaceutical and Medicinal Chemistry at the University of Würzburg, Germany

DNA-encoded libraries (DELs) are an exciting technology that enables screening ultra-large combinatorial collections of drug-like compounds on biological targets. However, synthesis methodology for library design is seriously limited to very few reactions due to the reactivity of DNA, aqueous co-solvents to dissolve DNA-tagged starting materials and the combinatorial workflow. We have developed a chemically more robust, yet fully functional genetic tag for DNA-encoded library synthesis and a polymeric solvent additive that solubilizes DNA tags in apolar, dry organic solvents such as dichloromethane, chloroform, and co-solvents. This combination of a more robust tag and a broader choice of solvents enabled high-yielding isocyanide multicomponent reactions (IMCRs) and ruthenium-promoted ring-closing metathesis (RCM) reactions with a broad reactant scope on DNA-tagged starting materials. During the synthesis of a 500.000-membered DNA-encoded library of macrocycles by RCM chemistry we established a workflow to produce sizable DELs in our laboratory. Successful screening of this DEL on targets demonstrated the functionality of the barcoding strategy and the compatibility of ruthenium catalysis with the DNA tag. The macrocycle DEL is part of a growing academic compound screening resource.

Short biography: Professor Andreas Brunschweiler is currently serving as the Chair of Pharmaceutical and Medicinal Chemistry at the University of Würzburg. He completed his PhD thesis mentored by Prof. Christa Müller at the University of Bonn in 2007. He had postdoctoral stays with Prof. Christa Müller and Prof. Jonathan Hall at ETH Zürich. From 2013 – 2022, he led an independent research group at TU Dortmund and received his *venia legendi*. His research is centred on drug discovery using DNA-encoded libraries. This involves development of DNA-barcoding strategies, exploring nanoheterogeneous reaction systems, expanding the scope of chemistry and designing, synthesizing and screening chemically diverse libraries.



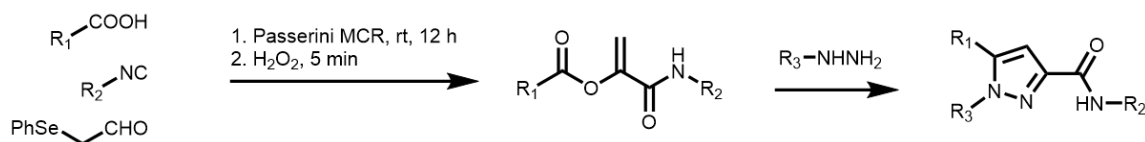
One-Pot Installation of Backbone-Embedded Pyrazoles in Peptides and its application to bioconjugation

Thimmalapura Marulappa Vishwanatha,^{a,b} Alexander Dömling^{a,b*}

^aRegional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic.

^bInstitute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic.

We developed a one-pot procedure for the synthesis of a dehydroalanine motif through a Passerini multicomponent reaction, followed by mild oxidation and spontaneous isomerization to generate a backbone-embedded α,γ -diketoamide via a formal O-to-C acyl shift. This strategy enables the efficient introduction of the dehydroalanine motif into small molecules and peptides using phenylselenoaldehyde as a key reagent. Subsequent incubation under physiological pH conditions promotes the conversion of the dehydroalanine motif into the corresponding α,γ -diketoamide. The resulting α,γ -diketoamide serves as a versatile functional handle for diversification with a range of hydrazines, enabling the formation of structurally diverse pyrazole derivatives. Importantly, these functional motifs remain directly embedded within the peptide backbone, providing access to structurally modified peptide scaffolds. The modularity of this approach, combined with mild reaction conditions and compatibility with miniaturized reaction formats, provides a practical platform for the rapid generation of diversified small-molecule and peptide libraries.



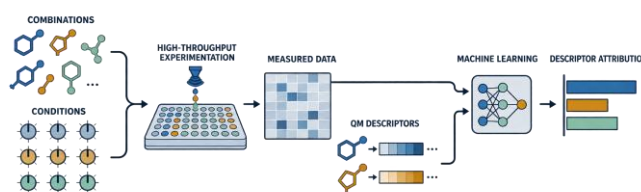
Reading a reaction space: quantum-chemical descriptors and machine learning for a triazolopiperazine library

Riccardo Fusco^{a,b}, Alexander Dömling^{a,b*}

^aRegional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic.

^bInstitute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic.

Chemistry is a two-axis design problem: which combination of building blocks works under which conditions. Together, those axes create a combinatorial explosion challenging to sample exhaustively. High-throughput experimentation turns that space into bench-quality experimental reaction data. Our triazolopiperazine library was built with this in mind. A sequential, expert-driven design of experiments sampled the conditions, while an in-house cherry-picking workflow assembled the chosen combinations into a measured dataset. Yet density alone is inert. A large record says nothing until something explains it.



Machine learning enters as the explanation engine. The model was trained to predict whether a designed combination gives a product from quantum-chemical descriptors of its two building blocks. For each building block, a quantum-chemical calculation supplied electronic, polarity, surface, size and shape quantities, together with atom-centred charges and reactivity indices. The atom-centred charges and indices were taken at the sites that react: the acid's carboxyl carbon and the aldehyde or ketone's carbonyl oxygen. The descriptors from both building blocks were combined into one description of the proposed reaction, pairing the carboxylic acid's properties with those of the carbonyl, so the model worked through chemical properties. We then look inside the trained model and attributed each decision back to named descriptors. This lets a chemist see which property of which building block moved the chemical result and read out patterns too fine to notice by eye.

Experimentation supplies the data; quantum-chemical descriptors make it readable. Together they turn a combination-condition matrix from a list to guess through into a space to navigate; the triazolopiperazine collection is one illustration.

Developing GAL3 Degraders for the Treatment of Alzheimer's Disease

Tryfon Zarganis-Tzitzikas^{1,2}

¹*Alzheimer's Research UK Oxford Drug Discovery Institute, Centre for Medicines Discovery, Nuffield Department of Medicine, Oxford, UK.*

²*Centre for Medicines Discovery, Nuffield Department of Medicine Research Building (NDMRB), University of Oxford, Oxford, UK.*

tryfon.zarganis-tzitzikas@cmd.ox.ac.uk

Galectin-3 (Gal3) is a secreted lectin upregulated in microglia associated with Alzheimer's disease (AD) pathology, where it acts as an endogenous ligand for TREM2 and promotes proinflammatory signalling and amyloid- β (A β) aggregation. Gal3 has been implicated in neuronal injury in several neurodegenerative and injury models, though its effects on neuronal survival appear context-dependent. Genetic deletion or pharmacological inhibition of Gal3 has been shown to attenuate microglial activation and reduce A β burden in AD mouse models, suggesting Gal3 as a candidate therapeutic target. We hypothesise that inhibiting Gal3–TREM2 binding, or degrading intracellular Gal3 to prevent its secretion, will reduce microglial-driven inflammation and preserve microglial homeostasis, representing a potential therapeutic strategy in AD.

Short biography: Tryfon received his PhD (cum laude) in Medicinal Chemistry from the University of Groningen in 2017, focusing on innovative multicomponent reactions and their applications in drug design. He then joined Syncom B.V. (now Symeres) as a medicinal chemist, contributing to an immuno-oncology collaboration with the University of Groningen. From 2014 to 2022, he also served as co-founder and CSO of TesisPharma B.V., developing novel synthetic routes to APIs. In 2018, he joined Alzheimer's Research UK Oxford Drug Discovery Institute (ODDI) at the University of Oxford where his research focuses on developing new treatments for dementia. Since 2024, he has been Head of Chemistry at the ODDI. He specializes in therapeutics for CNS disorders and rare diseases, leading interdisciplinary teams and advancing small molecule candidates from discovery to preclinical development.



From Reaction Discovery to Reaction Grammar: A Topology-Generating Split-Interrupted Oxo-Carboxylic Acid Multicomponent Reaction

Mayur Mukim^{1,2}, Fiorella Meneghetti³, Matteo Mori³, Alexander Dömling^{1,2*}

¹*Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic*

²*Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Hněvotínská 5, Olomouc, 779 00, Czech Republic*

³ *Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche, XtaLab, Via L. Mangiagalli 25, 20133 Milano, Italy*

We invented a split-interrupted oxo-carboxylic acid multicomponent reaction that converts oxo-carboxylic acids, bis-secondary amines and isocyanides into topology-divergent N,O-heterocycles. Systematic reaction-space mapping reveals a highly structured reactivity landscape in which oxo-acid identity dominates overall success, while specific oxo-acid–diamine pairings impose a second layer of compatibility. These relationships define an experimentally derived reaction grammar linking substrate features to product-forming probability. The combination of topology generation and reaction-space learning provide a framework for discovering, understanding and expanding multicomponent reaction manifolds.

Small Molecule LAG-3 Inhibitors Synergize with Anti-PD-L1 Therapy in Cancer Immunotherapy

Konrad Barnowski^a, Sylwia Wójcik^a, Wiktoria Bara^a, Bharath Dinakaran^a, Łukasz Skalniak^a, Marta Karpień^a, Justyna Kalinowska-Tłuścik^a, Marzena Lenart^b, Jacek Plewka^a

^a Faculty of Chemistry, Jagiellonian University, Gronostajowa 2, 30-387 Krakow, Poland

^b Department of Clinical Immunology, Institute of Pediatrics, Jagiellonian University Medical College, Krakow, Poland

Keywords: cancer immunotherapy, small molecule inhibitors, LAG-3, PD-L1

Abstract:

Immune checkpoint blockade has transformed cancer treatment; however, many patients exhibit limited or transient responses to current therapies. LAG-3 has emerged as a promising immunotherapeutic target that cooperates with the PD-1/PD-L1 axis in mediating T-cell exhaustion and tumor immune evasion. While most clinical approaches rely on monoclonal antibodies, small molecule inhibitors offer attractive advantages, including improved tissue penetration, lower manufacturing costs, and greater flexibility for combination therapies.

In this presentation, I will discuss our efforts toward the discovery and characterization of novel small molecule inhibitors targeting LAG-3. Particular attention will be given to the synergistic effects observed when these compounds are combined with anti-PD-L1 treatment. I will present structural, biophysical, and biological data supporting the mechanism of action of these inhibitors, including promising in vivo results demonstrating enhanced antitumor efficacy in mouse models following co-administration with anti-PD-L1 therapy. These findings highlight the potential of small molecule immune checkpoint modulators as next-generation agents for combination cancer immunotherapy.

Short biography:

Short biography: Dr. Jacek Plewka is a Principal Investigator at the Faculty of Chemistry, Jagiellonian University, Kraków, Poland. His research focuses on medicinal chemistry, small-molecule inhibitors, protein–protein interactions, and cancer immunotherapy, with particular interest in targets such as PD-1/PD-L1 and LAG-3.



Acknowledgements: This work has been supported by the National Science Center of Poland as part of the OPUS grant “Innovative small molecule inhibitors targeting LAG-3 and the MHCII complex for cancer immunotherapy” (grant number UMO-2024/53/B/NZ7/02801).

Multicomponent Reaction-Based Synthesis and Anticancer Screening of Novel Benzo[f]tetrazolo[1,5-a][1,4]diazepines

Samatha_Masineni^{1,2}, Shahrzad Mahdavi Aliabad^{1,2} Zhirui Guan^{1,2} Marianna Moro³, Tracey Pirali³, Ambra Grolla³, Alex Dömling^{1,2}

¹*Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic*

²*Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic.*

³*Department of Pharmaceutical Sciences, University of Piemonte Orientale, Largo Donegani 2, 28100 Novara, Italy*

Benzodiazepines (BZDs) represent a cornerstone in the pharmacological management of central nervous system (CNS) disorders, including anxiety, insomnia, and epilepsy. Acting as positive allosteric modulators of the GABA_A receptor, BZDs enhance inhibitory neurotransmission by increasing chloride channel opening frequency¹. Despite their high therapeutic efficacy and favorable safety profile compared to historical sedatives, their clinical utility is frequently limited by the development of tolerance, physical dependence, and cognitive impairment^{2,3}.

Despite their established clinical utility, the exploration of rigidified, bio isosteric derivatives in oncology remains a frontier for therapeutic development. In this study, we report a novel, one-step multicomponent reaction (MCR) for the efficient synthesis of benzodiazepine derivatives incorporating a strategic benzo[f]tetrazolo[1,5-a][1,4] diazepine modification. This high-throughput methodology was developed to be fully compatible with Echo acoustic liquid handling systems, enabling rapid, scalable compound generation with nanolitre precision and reduced reagent consumption.

The synthesized library exhibited sub micromolar potency, demonstrating superior anti-proliferative activity compared to the gold-standard BET inhibitor JQ1. The enhanced potency is attributed to the synergistic effects of the benzodiazepine scaffold and the tetrazole bio isostere, which likely optimize molecular interactions and improve metabolic stability. Overall, this work introduces a robust, automated synthetic platform and identifies a promising new class of anticancer candidates, establishing the tetrazolo-fused benzodiazepine framework as a high-value scaffold for future drug discovery.

DEVELOPMENT OF TMP-0193: A NOVEL MODULATOR OF CARDIAC DIASTOLIC FUNCTION

Thiago Moreira Pereira,^{1,2} Anthony Hessel,³ Andrew Hladký,⁴ Brad Palmer,⁵ and Alexander Domling^{1,2,4}

¹Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute (CATRIN), Palacký University Olomouc, Šlechtitelů 27, Olomouc, 783 71, Czech Republic. ²Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic.

³Accelerated Muscle Biotechnologies, Hamburg, Germany and Boston, MA USA.

⁴AMADTEUS GmbH, Hamburg, Germany. ⁵Sarcometrics LLC, Burlington, VT USA.

Heart failure with preserved ejection fraction (HFpEF) currently represents a major and growing clinical challenge, accounting for approximately 40–50% of heart failure cases and lacking effective therapeutic options.^{1–3} A key pathological feature of HFpEF is impaired diastolic relaxation, often associated with altered calcium handling and/or dysregulated sarcomeric protein function. In this context, the identification of small molecules capable of improving myocardial relaxation represents an important therapeutic strategy.^{2,4}

In this work, we evaluated a series of compounds - derived from the AMADTEUS technology platform - using cardiac slice model prepared from ZSF1-Obese rats known to have diastolic dysfunction (Figure 1A). Contractile performance was assessed through isometric force transients under controlled conditions (2 or 3 Hz stimulation frequency, 35°C, 2.5 mM extracellular Ca²⁺, sarcomere length 1.9–2.0 μm). Key transient characteristics examined included developed force (F_{dev}), time to peak contraction and relaxation times (50% and 90% return), as well as rates of force development and decay (dF/dt max and min) (Figure 1B). Among the compounds tested, **TMP-0193** demonstrated a significant enhancement in diastolic function, characterized by shortened relaxation times and, in some cases, increased contractile performance whereas there were no changes in these parameters in controls. These effects were reproducible across multiple measurements. Notably, the observed phenotype closely resembles the effects induced by β-adrenergic stimulation (e.g., isoprenaline), suggesting a possible involvement of signalling pathways that regulate calcium regulation and sarcomere mechanics (Figure 1B).

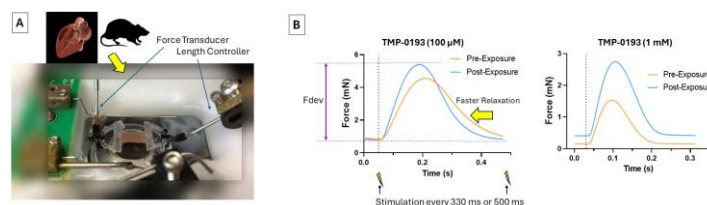


Figure 1. (A) Heart tissue assay; (B) Modulation effect of TMP-0193.

In conclusion, **TMP-0193** represents a promising lead compound for the modulation of diastolic function, with potential relevance for HFpEF treatment. Comprehensive mechanistic validation to distinguish between direct sarcomeric effects and indirect signalling-mediated pathways and potential off-target liabilities are currently ongoing.

MCRs: Unlocking Chemical Space

From Molecular Diversity to Function and New Modalities

Dinos Neochoritis

Chemistry Department, University of Crete, Heraklion, Greece



It is truly remarkable to witness how Multicomponent Reactions (MCRs) have evolved and found their unique place in the world of organic chemistry. Once considered unconventional “outcasts” whose beauty and potential were not fully appreciated, MCRs have emerged as powerful platforms for generating molecular diversity, exploring chemical space, and rapidly constructing complex functional architectures. What fascinates us most is their remarkable ability to continuously adapt as new frontiers emerge in chemistry. MCRs are not confined to a particular era or application; they continue to find opportunities across many of the trends shaping modern chemistry, from drug discovery and chemical biology to atropisomerism, molecular glues, PROTACs, materials science, biocatalysis, electrochemistry and mechanochemistry.

In this talk, I will present how our research exploits MCRs not simply as synthetic tools, but as platforms for molecular discovery. I will highlight our efforts to develop new reaction manifolds, access structurally and stereochemically complex molecular architectures, explore biological function and ultimately connect molecular diversity with emerging therapeutic modalities. The journey is therefore not only about making more molecules, but about discovering what these molecules can do.

Short biography: Short BioProf. Dr. Constantinos G. Neochoritis is an Associate Professor in the Department of Chemistry at the University of Crete, Greece. He received his Ph.D. in Organic Chemistry from the Aristotle University of Thessaloniki in 2011. He subsequently conducted postdoctoral research in Medicinal Chemistry at Aristotle University and in Medicinal/Organic Chemistry and Drug Design at the University of Groningen, Netherlands, under Prof. Alexander Dömling. His current research focuses on multicomponent reactions, medicinal chemistry, novel chemical modalities, bioactive molecules, and high-throughput synthesis.



CZECH-GEN is a Czech chemical-pharmaceutical company with a long-standing tradition. It focuses on the research, development and manufacture of active pharmaceutical ingredients (APIs), intermediates and chemical specialties. APIs account for up to 95% of its sales, and the company supplies them to customers in more than 80 countries, including highly regulated markets.

Development and manufacturing are carried out under cGMP conditions, in quantities ranging from several grams to hundreds of kilograms. The 36,000 m² manufacturing site includes two cGMP production facilities and related operations. Modern analytical equipment enables precise characterization of substances and thorough verification of their purity.

Thanks to its experienced team and strong technological background, CZECH-GEN offers comprehensive services in contract research and custom manufacturing under CMO and CDMO models. It is therefore able to respond flexibly to customer needs at individual stages of development and manufacturing.

In 2026, the company changed its original name FARMAK to CZECH-GEN. The new brand combines Czech quality in the first part of the name, while the GEN part represents the intergenerational continuity of the family-owned company and, at the same time, refers to the manufacture of active ingredients for generic medicines. Under its new name, the company builds on decades of experience and opens a new stage of its development.



CZECH-GEN je česká chemicko-farmaceutická společnost s dlouholetou tradicí. Zaměřuje se na výzkum, vývoj a výrobu účinných léčivých látek (API), meziproduktů a chemických specialit. API představují až 95 % jejich tržeb a společnost je dodává zákazníkům ve více než 80 zemích, včetně vysoce regulovaných trhů.

Vývoj a výroba probíhají v režimu cGMP, a to v objemech od několika gramů až po stovky kilogramů. Výrobní areál o rozloze 36 000 m² zahrnuje dvě cGMP výrobní haly a související provozy. Moderní analytické vybavení umožňuje přesnou charakterizaci látek a důsledné ověřování jejich čistoty.

Díky zkušenému týmu a silnému technologickému zázemí nabízí CZECH-GEN komplexní služby v oblasti smluvního výzkumu a zakázkové výroby v režimech CMO a CDMO. Dokáže tak pružně reagovat na potřeby zákazníků v jednotlivých fázích vývoje i výroby.

V roce 2026 společnost změnila svůj původní název FARMAK na CZECH-GEN. Nová značka spojuje v první části názvu českou kvalitu, zatímco část GEN mezigenerační kontinuitu rodinné firmy a zároveň také odkazuje na výrobu účinných látek pro generická léčiva. Pod novým jménem společnost staví na desetiletích zkušeností a otevírá další etapu svého rozvoje.



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