

MMCS
2026
Conference

The 5th Molecules Medicinal Chemistry Symposium

14–17 May 2026 | Beijing, China



Program and Abstract Book

Organizers



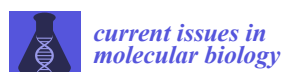
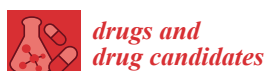
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Complimentary Wi-Fi is available at the conference venue:

- Network (SSID): BYDJD
- Password: 84932266

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Please scan the QR code to view live conference photos.

Latest Program

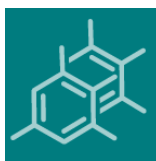
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Conference Secretariat

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molecules

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Molecules (ISSN 1420-3049, CODEN: MOLEFW) provides an advanced forum for science of chemistry and all interfacing disciplines. Our aim is to provide rigorous peer review and enable rapid publication of cutting-edge research to educate and inspire the scientific community worldwide. Scientists are encouraged to publish their experimental and theoretical results in as much detail as possible. There is no restriction on the maximum length of the papers. Full experimental details must be provided so that the results can be reproduced. In addition, the availability of compound samples is published and considered important information, and authors are encouraged to register or deposit their chemical samples.

Impact Factor: 4.6 (2024); 5-Year Impact Factor: 5.0 (2024)

General Information

Conference Venue

Beiyuan Grand Hotel, Beijing

Address: Building A6, Shuangying Road, Chaoyang District, Beijing.



The conference will be held at Beiyuan Grand Hotel, located in the Asian Games Village and Olympic Sports Center area, with the renowned China Science and Technology Museum and Olympic Forest Park nearby.

Registration & Dining:

Registration: 1st Floor Lobby, May 14

Lunch: 1st Floor Four Seasons Restaurant, May 15–17

Banquet Dinner: 3rd Floor Ballroom, May 15

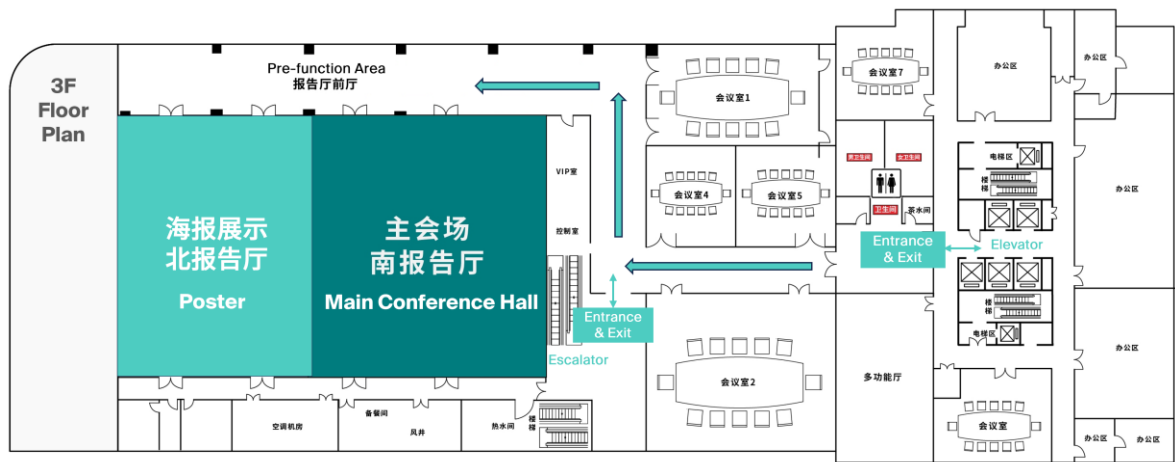
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Insurance

The organizers shall not be liable for any personal accidents or property loss.

Main Conference Hall
3rd Floor, Beiyuan Grand Hotel



Route to the Venue

By Plane

1. Getting from Beijing Daxing International Airport (PKX) to the venue

- By metro:

Duration: approx. 1 hour 40 minutes

Daxing Airport Line (Entrance A) → Caoqiao Station on Line 19 → Mudanyuan Station on Line 10 (Inner Loop) → Huixin Xijie Nankou Station on Line 5 → BeiYuan North Road Station (Exit B2)

- By taxi:

Duration: approx. 1 hour 30 minutes (traffic dependent)

Estimated Fare: CNY 239

2. Getting from Beijing Capital International Airport (PEK) to the venue

- By metro:

Duration: approx. 1 hour 30 minutes

Capital Airport Line (North Entrance) → Sanyuanqiao Station on Line 10 → Huixin Xijie Nankou Station on Line 5 → BeiYuan North Road Station (Exit B2)

- By taxi:

Duration: approx. 50 minutes (traffic dependent)

Estimated Fare: CNY 80

By High-Speed Rail

1. Getting from the Beijing West Railway Station to the venue

- By metro:

Duration: approx. 1 hour 10 minutes

Line 7 from Beijing West Railway Station → Ciqikou Station on Line 5 → BeiYuan North Road Station (Exit B2)

- By taxi:

Duration: approx. 50 minutes (traffic dependent)

Estimated Fare: CNY 80

2. Getting from the Beijing South Railway Station to the venue

- By metro:

Duration: approx. 1 hour 15 minutes

Line 14 from Beijing South Railway Station → Puhuangyu Station on Line 5 → BeiYuan North Road Station (Exit B2)

- By taxi:

Duration: approx. 56 minutes (traffic dependent) Estimated Fare: CNY 90

The 5th Molecules Medicinal Chemistry Symposium

14–17 May 2026 | Beijing, China



Organizing Committee

Conference Chairs

Prof. Dr. Xiaoguang Lei
Prof. Dr. Diego Muñoz-Torrero

Chair of the Scientific Committee

Prof. Dr. Lihe Zhang

Scientific Committee

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Welcome from the Chairs

We are delighted to announce The 5th Molecules Medicinal Chemistry Symposium (MMCS 2026): New Trends in Chemical Biology and Drug Discovery, which will take place in Beijing, China, from 14–17 May, 2026.

MMCS 2026 is proudly organized by MDPI, the esteemed publisher of the open-access journal *Molecules*. Building on the outstanding success of previous events held in Rome and Barcelona, this symposium continues our commitment to pushing the boundaries of chemical biology and drug discovery. This year offers an engaging and comprehensive program, highlighting the latest advancements and exploring cutting-edge topics:

Session 1: Chemical Biology for Drug Discovery
Session 2: Medicinal Chemistry Tales
Session 3: Natural Products in Drug Discovery
Session 4: AI for Drug Discovery
Session 5: Drug Discovery Targeting GPCRs and Ion Channels
Session 6: New Proximity-Based Drug Modalities
Session 7: Biocatalysis for Natural Product and Drug Synthesis

Each session will feature distinguished keynote speakers, sharing their groundbreaking insights and latest research findings. Complementing these presentations, selected talks from promising young researchers and poster sessions will offer a platform for emerging scientists to showcase their innovative work and contribute to this vibrant exchange of ideas.

Beijing provides an inspiring setting for this prestigious event. With a blend of rich cultural heritage and cutting-edge innovation, the city offers the perfect backdrop for participants to engage in thought-provoking discussions on research innovation whilst also exploring the beauty of one of the world's most captivating places in the spring-time.

We would be delighted to welcome you to Beijing for what promises to be an enlightening and impactful symposium. Together, let us explore new horizons, foster collaboration, and shape the future of chemical biology, medicinal chemistry, and drug discovery.



Prof. Dr. Xiaoguang Lei
Conference Chair

College of Chemistry and Molecular Engineering,
Peking University,
Beijing, China



Prof. Dr. Diego Muñoz-Torrero
Conference Chair

Faculty of Pharmacy and Food Sciences, and the Institute of Biomedicine (IBUB), University of Barcelona, Barcelona, Spain

Plenary Speakers



Prof. Dr. Dawei Ma
Shanghai Institute of Organic
Chemistry, CAS,
Shanghai, China

Dr. Dawei Ma received his PhD in 1989 from Shanghai Institute of Organic Chemistry (SIOC), and did his postdoctoral studies at the University of Pittsburgh and Mayo Clinic. He returned to SIOC in 1994, and was appointed as research professor in 1995. From 2001 to 2010 he was the director of State Key Laboratory of Bioorganic & Natural Products Chemistry. He is presently director of drug discovery center at Institute of Oncology and Basic Medicine, Chinese Academy of Sciences. His research mainly focuses on the total synthesis of complex natural products and structure-activity relationships, as well as synthetic methodology and its applications in the synthesis of biologically active molecules. He has improved the Ullmann reaction, solving the long-standing scientific challenge of constructing carbon-heteroatom bonds, and his achievements have been widely applied in the discovery of new drugs and the development of new materials.



Prof. Dr. Richard DiMarchi
Indiana University, Bloomington,
IN, USA

Richard DiMarchi is a Distinguished Professor of Chemistry and Gill Chair in Biomolecular Sciences at Indiana University. He is a member of the National Academy of Medicine and the National Inventors Hall of Fame. Dr. DiMarchi served as a Group Vice President at Eli Lilly and later at Novo Nordisk. He is recognized for his contributions to the discovery and development of rDNA-derived Humulin®, Humalog®, rGlucagon®, and Forteo®. His academic research has broadened the understanding of glucagon and incretin physiology and pioneered the discovery of single molecule multi-mechanism agonists for the treatment of diabetes and obesity. The central element to success has been the chemical vision and technology to install within single molecules simultaneous agonism, related G-protein-coupled receptors, coupled to the counter-intuitive discovery that glucagon and GIP agonism could synergize the therapeutic efficacy of GLP-1. These peptides and the conceptual approach have transformed the management of excessive body weight to a condition comparable to how hypertension, adult-onset diabetes, and excess cholesterol are medically managed.



Prof. Dr. Xiaoguang Lei
College of Chemistry and Molecular Engineering,
Peking University,
Beijing, China

Prof. Xiaoguang Lei earned a BS in Chemistry from Peking University (2001) and a PhD in organic synthesis from Boston University under Prof. John Porco (2006). He conducted postdoctoral research in bioorganic chemistry with Prof. Samuel Danishefsky at Columbia University (2006–2008). Returning to China in 2009, he became Principal Investigator and Director of the Chemistry Center at the National Institute of Biological Sciences, Beijing. Since 2014, he has been a tenured full professor at Peking University and is now the Boya Distinguished Professor of Chemistry and Chemical Biology, a senior PI at the Peking-Tsinghua Center for Life Sciences, and a PI of the New Cornerstone Science Laboratory. His research focuses on chemical biology, biocatalysis, synthetic biology, and drug discovery. He has received numerous prestigious awards, including the 2025 BMS Lectureship Award at Yale, the 2023 Sackler Chair Visiting Scholar Award, the 2022 Molecules Tu Youyou Award and Xplore Prize, the 2021 Boehringer-Ingelheim Senior Investigator Award, the 2020 Bayer Investigator Award, and earlier honors such as the 2018 David Ginsburg Award, the 2017 Tetrahedron and Swiss Chemical Society Distinguished Lectureship Awards, the 2015 Chemical Society of Japan Distinguished Lectureship Award, the 2014 Roche Young Investigator Award, the 2013 ICBS Young Chemical Biologist and Servier Young Investigator Awards, and the 2010 IUPAC Young Chemist Award, etc.

Keynote Speakers



Dr. Albert Antolin Hernandez
Vall d'Hebron Institute of Oncology Health Department, University of Caen Normandy, Caen, France



Prof. Dr. Christophe Rochais
Health Department, University of Caen Normandy, Caen, France



Prof. Dr. Hiroshi Abe
Department of Chemistry, Nagoya University, Nagoya, Japan



Prof. Dr. Hong Liu
Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China



Prof. Dr. Kewu Zeng
School of Pharmaceutical Sciences, Peking University, Beijing, China



Prof. Dr. Jason Micklefield
Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London, UK



Prof. Dr. Jianjun Cheng
School of Life Science and Technology, ShanghaiTech University, Shanghai, China



Prof. Dr. Ke Ding
Shanghai Institute of Organic Chemistry, CAS, Shanghai, China



Prof. Dr. Luhua Lai
College of Chemistry and Molecular Engineering (CCME), Peking University, Beijing, China



Prof. Dr. Motonari Uesugi
Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Kyoto, Japan



Prof. Dr. Ting Han
National Institute of Biological Sciences, Beijing, China



Prof. Dr. Wen Liu
Shanghai Institute of Organic Chemistry, CAS, Shanghai, China



Prof. Dr. Xiaojie Lu
Shanghai Institute of Materia Medica, CAS, Shanghai, China



Prof. Dr. Xinjing Tang
School of Pharmaceutical Sciences, Peking University, Beijing, China



Prof. Dr. Yefeng Tang
Department of Pharmacology and Pharmaceutical Sciences, Tsinghua University, Beijing, China

Chair of the Scientific Committee



Prof. Dr. Lihe Zhang
Peking University,
Beijing, China

Prof. Dr. Lihe Zhang, Professor at Peking University, an Academician of the Chinese Academy of Sciences (CAS) and a distinguished chemical biologist and medicinal chemist, and the Honorary Director of the Academic Committee of the State Key Laboratory of Natural and Biomimetic Drugs. He is also a pioneering advocate of chemical biology in China. Prof. Lihe Zhang graduated from the Department of Pharmacy of Beijing Medical College (now part of Peking University) in 1958. Since 1985, he has been a professor in the School of Pharmaceutical Sciences, Beijing Medical University (1985-1999) and Peking University (2000-present). He served as the dean of the School of Pharmaceutical Sciences from 1987 to 1999 and as the director of the Chemistry Department of the National Natural Science Foundation of China from 1999 to 2006. He is an international editor for *Org. Biomol. Chem.*, *ChemMedChem*, *Curr. Top. Med. Chem.*, and *Med. Res. Rev.*; the chief editor of *Chin. J. Med. Chem.*; the deputy chief editor of *Chem. J. Chin. Univ.* and *Eur. J. Med. Chem.* His research focused on nucleic acid chemistry, anti-tumor and antiviral drugs, systematic studies on the structures and biological activities of intracellular signaling molecule cADPR and cAMP, the cleavage mechanism of enzymatic nucleic acids, structural modification and recognition of oligonucleotides, and synthesis of nucleosides and nucleotides for antitumor and antiviral drugs.

Scientific Committee



Prof. Dr. Andrea Trabocchi
University of Florence, Firenze, Italy



Prof. Dr. Chao Wang
Soochow University, Suzhou, China



Prof. Dr. Chun Li
Tsinghua University, Beijing, China



Prof. Dr. Daofeng Chen
Fudan University, Shanghai, China



Prof. Dr. Eva de Lago Femia
Complutense University of Madrid,
Madrid, Spain



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Universitat Jaume I,
Castelló de la Plana, Spain



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East China University of Science and
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Kong, China



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University of Reading, Reading, UK



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East China Normal University,
Shanghai, China



Prof. Dr. Huilei Yu
East China University of Science
and Technology, Shanghai, China



Prof. Dr. Huiming Ge
Nanjing University, Nanjing, China



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Former Head of the Department of
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Mons-UMONS, Mons, Belgium



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USA



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University of Innsbruck,
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National Institute of Biological Sci-
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Zhejiang University, Hangzhou, China



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Shandong University, Jinan, China



Prof. Dr. Qidong You
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Sapienza University of Rome, Rome,
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Moscow, Russia



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Changsha, China



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National Research Council (CNR),
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Prof. Dr. Yuanqiang Guo
Nankai University, Tianjin, China



Prof. Dr. Yujun Zhao
Zhejiang University of Technology,
Hangzhou, China



Prof. Dr. Zhongwu Guo
University of Florida, Gainesville, FL,
USA



Prof. Dr. Zhenjun Yang
Peking University, Beijing, China

Program Overview

	14 May 2026 Thursday	15 May 2026 Friday	16 May 2026 Saturday	17 May 2026 Sunday
Morning		Registration (8:00–9:00)	Registration (8:00–9:00)	Registration (8:00–9:00)
		Opening Ceremony	Plenary Talk	Session 6
		Plenary Talk		
		Tea break	Tea break	Tea break
		Session 1	Session 3	Session 6
		Lunch Break	Lunch & Poster Session	Lunch Break
Afternoon	Registration (15:00–17:30)	Session 1	Session 3	Session 6
			Session 4	Session 7
		Tea break	Tea break	Tea break
		Session 2	Session 4	Session 7
		Poster Session	Session 5	Award and Closing Ceremony
		Banquet Dinner		

Please scan the QR code to check the latest program.



MMCS 2026 Program

14 May 2026 (Thursday)		
Time: 15:00 (CST, China) Main Venue (Beiyuan)		
CST Time	Speaker	Title
15:00–17:30	Check-In & Onsite Registration	
15 May 2026 (Friday)		
Time: 8:00 (CST, China) Main Venue (Beiyuan)		
CST Time	Speaker	Title
8:00–9:00	Check-In & Onsite Registration	
9:00–9:20	Opening Ceremony	
9:20–10:00	Dawei Ma Plenary Speaker	Total Synthesis and SAR Studies of Some Bioactive Natural Products
10:00–10:40	Richard DiMarchi Plenary Speaker	Learn, Unlearn, Relearn - A Formula to Transformative Peptide Therapeutics
10:40–11:10	Tea Break	
	Session 1. Chemical Biology for Drug Discovery	
11:10–11:15	Session Introduction	
11:15–11:45	Hiroshi Abe Keynote Speaker	Molecular Design of mRNA Based on Chemistry and its Utilization in Drug Discovery Technology
11:45–12:00	Xavier Fernández-Busquets Oral Presenter	A Family of Compounds Highly Potent against Plasmodium and Leishmania with a Novel Mechanism of Action Targeting Protein Condensates
12:00–12:15	Xiaohui Liu Oral Presenter	G3BP1/2-Targeting PROTAC Disrupts Stress Granules Dependent ATF4 Migracytosis as Cancer Therapy
12:15–13:30	Lunch	
	Session 1. Chemical Biology for Drug Discovery	
Time: 13:30 (CST, China) Main Venue (Beiyuan)		
CST Time	Speaker	Title
13:30–14:00	Xinjing Tang Keynote Speaker	Chimeric Oligonucleotide drugs for targeting RNA and protein degradation
14:00–14:15	Gelin Wang Oral Presenter	Pharmacological Activation of NAD ⁺ Biosynthesis for Neuroprotection
14:15–14:30	Yun Shi Oral Presenter	Small Molecules Reveal Molecular Mechanisms of SARM1 Activation and Inhibition
14:30–14:45	Huiyuan Meng Oral Presenter	Fragment-Induced Enhancement of Extracellular Growth via Metabolic Reprogramming
14:45–15:15	Tea Break	

Session 2. Medicinal Chemistry Tales

15:15–15:20	Session Introduction	
15:20–15:50	Hong Liu Keynote Speaker	Artificial Intelligence Driven CCR5 Antagonist Discovery and Development
15:50–16:05	Antonello Mai Oral Presenter	Discovery of Covalent and Non-covalent Isoform-Selective NADPH Oxidase Inhibitors through Ultra-Large Virtual Screening and Medicinal Chemistry Optimization: New Tools for Cancer and Neuroprotection
16:05–16:20	Shujing Xu Oral Presenter	Discovery and Mechanism Study of Novel HBV CpAMs with High Potency and Broad Anti-drug Resistance Activity
16:20–16:35	Axel Klein Oral Presenter	Functionalizing Thiosemicarbazones for Biomedical Targets
16:35–16:50	Ana Mallo-Abreu Oral Presenter	Discovery of a Novel Class of Potent Inhibitors of the m6A Demethylase FTO for the Treatment of Severe CNS Disorders
16:50–17:05	Ke Ding Keynote Speaker	Chemical Adaptation in Kinase Drug Design
17:05–18:30	Poster Session	
18:30	Banquet Dinner	

16 May 2026 (Saturday)**Session 3. Natural Products in Drug Discovery****Time: 9:00 (CST, China) | Main Venue (Beiyuan)**

CST Time	Speaker	Title
9:00–9:40	Xiaoguang Lei Plenary Speaker	Translational Chemical Biology
9:40–9:45	Session Introduction	
9:45–10:15	Motonari Uesugi Keynote Speaker	Small Molecules that Potentiate Antitumor Immunity
10:15–10:30	Fusheng Guo Oral Presenter	Discovery and Total Synthesis of Anhydrotuberosin as a STING Antagonist for Treating Autoimmune Diseases
10:30–11:00	Tea Break	
11:00–11:30	Yefeng Tang Keynote Speaker	Natural Product-Driven Innovative Drug Discovery
11:30–11:45	Jun-Li Yang Oral Presenter	Natural Product AW126 Inhibits Pancreatic Cancer Growth via TGF- β /MAPK Pathway
11:45–12:00	Alejandro Calderon-Urrea Oral Presenter	Identification of Chalcone 17 and Chalcone 30 Protein Targets in the nematode <i>Caenorhabditis elegans</i> : new nematocides mode of action (MOA)
12:00–12:15	Xiaowei Luo Oral Presenter	Anti-osteoporosis Lead Compounds from Marine Fungi
12:15–13:30	Lunch & Poster Session	
13:30–14:00	Kewu Zeng Keynote Speaker	Identification of Cellular Targets for Natural Bioactive Molecules
14:00–14:15	Zhengfeng Fan Oral Presenter	Triptolide Enhances Valve Interstitial Cell Autophagy-Lysosomal Function to Alleviate Calcific Aortic Valve Disease

Session 4. AI for Drug Discovery**Time: 14:15 (CST, China) | Main Venue (Beiyuan)**

CST Time	Speaker	Title
14:15-14:20	Session Introduction	
14:20-14:50	Albert Antolin Hernandez Keynote Speaker	A Small Molecule Targeting Every Human Protein: Harnessing AI to Realize the Dream
14:50-15:05	Niu Huang Oral Presenter	Integrating HPC and AI to Advance Protein-ligand Binding Interaction Prediction
15:05-15:20	Rino Ragno Oral Presenter	Machine Learning Approaches for Predicting ADMET Parameters in Drug Development: Integrating Molecular Descriptors and Deep Learning
15:20-15:50	Tea Break	
15:50-16:20	Luhua Lai Keynote Speaker	Drug Discovery towards Undruggable Targets
16:20-16:35	Yao Wu Oral Presenter	Assessment of Affinity Prediction Approaches in Small Molecular Drug Discovery

Session 5. Drug Discovery Targeting GPCRs and Ion Channels

16:35-16:40	Session Introduction	
16:40-17:10	Jianjun Cheng Keynote Speaker	Psychedelics-inspired Drug Discovery: Structure-based Design of Subtype-selective 5-HT _{2A} Agonists
17:10-17:25	Miao Jing Oral Presenter	Photocrosslinking-assisted Platform for GPCR Deorphanization and Related Drug Discovery
17:25-17:40	Mariana Spetea Oral Presenter	Selective Activation of the Kappa-opioid Receptor by Diphenethylamines, HS665 and HS666, for an Effective and Safer Pain Treatment
17:40-17:55	Qiong Xie Oral Presenter	Discovery of Novel Adenosine A _{2A} /A _{2B} Dual Antagonists for Cancer Immunotherapy
17:55-18:25	Christophe Rochais Keynote Speaker	Beyond Single Targets: Serotonin System Polypharmacology and Prodrug Development in Alzheimer's Disease

17 May 2026 (Sunday)**Session 6. New Proximity-Based Drug Modalities****Time: 9:00 (CST, China) | Main Venue (Beiyuan)**

CST Time	Speaker	Title
9:00-9:05	Session Introduction	
9:05-9:35	Xiaojie Lu Keynote Speaker	DNA Encoded Library Technology Development and its Application for Proximity -Based Drug Discovery
9:35-9:50	He Chen Oral Presenter	Extracellular HSP90-Facilitated Degradation of Extracellular and Membrane Proteins by Bifunctional Small Molecules
9:50-10:05	Chengliang Zhu Oral Presenter	Targeting E3 Pseudoligases via Proximity-Based Protein Abundance Control: TRIM15 as a Case Study
10:05-10:20	Yudao Shen Oral Presenter	RIMTAC: A Novel Degradation Design Platform by Indirect VHL-Recruitment via RIPK1
10:20-10:35	Zhenyi Hu Oral Presenter	Hijacking Phosphatases for Target Protein Dephosphorylation with Phosphorylation Targeting Chimeras (PhosTACs)

10:35–11:05	Tea Break	
11:05–11:20	Xufen Yu Oral Presenter	PSMA-Mediated Target Protein Degradation Enables Selective and Effective Therapy for Prostate Cancer
11:20–11:35	Lei Wang Oral Presenter	Proximity-Based Small Molecules for Induced Dephosphorylation
11:35–11:50	Javier Sánchez Oral Presenter	Targeted Degradation of TDP-43: A PROTAC-Based Therapeutic Approach for ALS and Alzheimer’s Disease
11:50–12:05	Zunhua Yang Oral Presenter	Synthesis of PTP1B-Targeting PROTACs and Their Anti-Type 2 Diabetes Activity
12:05–13:30	Lunch	
Session 6. New Proximity-Based Drug Modalities		
Time: 13:30 (CST, China) Main Venue (Beiyuan)		
CST Time	Speaker	Title
13:30–14:00	Ting Han Keynote Speaker	Molecular Glue Degraders: Discovery and Therapeutic Potential
14:00–14:15	Xiaowen Xie Oral Presenter	The Converging Mechanism of a Molecular Glue Degradator and Cancer Gain-of-function Mutations
14:15–14:30	Xiulei Mo Oral Presenter	Targeting the “Undrugged” SMAD4 Protein with Mutation-directed Molecular Glues
14:30–14:45	Hai Wang Oral Presenter	Novel Nanodrug Based on Proximity Effect
Session 7. Biocatalysis for Natural Product and Drug Synthesis		
14:45–14:50	Session Introduction	
14:50–15:20	Wen Liu Keynote Speaker	Biosynthesis of Enethioether Crosslinked, Peptide Natural Products
15:20–15:35	Kangdelong Hu Oral Presenter	Novel Oxidative Amidases for the Efficient Synthesis of Amides
15:35–16:05	Tea Break	
16:05–16:20	Dongshan Wu Oral Presenter	Merging Natural and Unnatural Reactivity of Reductive Aminases for Stereoselective Thioamination Cascade Reactions
16:20–16:35	Sihua Hou Oral Presenter	Convergent Total Synthesis and Structural Revision of (–)-Papillone A via Pd-Catalyzed Alkenylation/Cyclization Cascade
16:35–16:50	Yihua Chen Oral Presenter	Biosynthesis and Chemoenzymatic Synthesis of ADP-heptoses
16:50–17:05	Licheng Yang Oral Presenter	Biocatalytic Synthesis of Chiral Amines toward Novel Drug Discovery
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Session 1. Chemical Biology for Drug Discovery

sciforum-163086: Fragment-Induced Enhancement of Extracellular Growth via Metabolic Reprogramming

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In vitro cell culture is a fundamental tool in biomedical research, providing a controlled and reproducible environment for studying cellular behaviour. Foetal bovine serum (FBS) is widely used as a supplement in culture media due to its rich supply of nutrients and growth factors. However, ethical concerns regarding its collection, high cost, and significant batch-to-batch variability have driven efforts to reduce FBS dependence in cell culture systems.

The Maybridge fragment library consists of small molecular fragments (MBFs) that follow the Rule of Three (RO3) and structurally resemble drug. Due to their drug-like properties, these fragments may interact with cellular metabolic pathways and potentially mimic or complement the functions of chemical drugs in supporting cell growth. This study therefore aimed to investigate whether MBFs can exert additive effects to enhance extracellular cell growth under reduced-serum conditions, and to explore the underlying metabolic mechanisms.

Cell viability of pancreatic cancer cell line Panc-1 was evaluated using the MTT assay, cell number was quantified using haemocytometer counting. Flow cytometry was conducted for cell cycle analysis, and RT-qPCR was performed to assess gene expression associated with metabolic regulation.

Treatment with 10 μ M MBF 3 significantly increased Panc-1 cell viability in medium containing 6% FBS compared with the standard 10% FBS condition. Notably, expression of pyruvate dehydrogenase kinase 1(PDK1) was significantly upregulated, indicating a Warburg metabolic shift away from oxidative phosphorylation. Together, these findings suggest that MBF3 can promote extracellular cell growth through metabolic reprogramming, highlighting their potential as additives for developing more sustainable and cost-effective in vitro culture systems with reduced reliance on FBS.



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sciforum-176340: AI-Assisted Structure–Activity Relationship Analysis of Functionalized Polyene Amide Derivatives for Neuroprotection Against Ischemic Injury

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Introduction

Ischemic stroke remains a major cause of neuronal injury and disability worldwide, and effective neuroprotective agents are still limited. Natural polyene compounds possess antioxidant and neuroregulatory properties; however, systematic investigation of polyene amide derivatives has been insufficient. This study aimed to construct a focused library of functionalized polyene amides and evaluate their neuroprotective potential using an interpretable artificial intelligence (AI)-assisted structure–activity relationship (SAR) approach.

Methods

Twenty polyene amide derivatives were synthesized via amide coupling between representative polyene acids and structurally diverse amines. Neuroprotective activity was assessed at 10 μ M using an oxygen–glucose deprivation (OGD) model in HT22 hippocampal neuronal cells. An Attentive FP-based graph attention neural network was applied to analyze atomic attention weights and interpret key structural features contributing to activity.

Results

Among the tested compounds, C5 and C12 exhibited the strongest neuroprotective effects, increasing cell viability by 18.99% and 13.42% compared with the OGD group, respectively. Both compounds demonstrated superior cellular efficacy compared to the clinical antioxidant drug Edaravone under identical conditions. AI-assisted SAR analysis indicated that the extended π -conjugated polyene backbone and catechol-containing moieties contributed most significantly to bioactivity.

Conclusions

This study integrates synthetic medicinal chemistry with interpretable AI modeling to accelerate neuroprotective lead discovery. Compounds C5 and C12 are promising candidates for further in vivo validation and mechanistic investigation.



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sciforum-180657: Cryoprotective Effects of Capsaicin and Its Therapeutic Potential Against Cold Stress

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As global climate change intensifies, extreme temperature stress poses an increasing threat to human health, particularly in the context of cold-related injuries and metabolic disorders. Exploring new therapeutic applications for existing compounds has emerged as a promising strategy in drug development. Capsaicin, a naturally occurring vanilloid derived from chili peppers, is well known for its analgesic and anti-inflammatory properties, yet its potential as a cryoprotective agent remains largely unexplored.

In this study, we employed *Caenorhabditis elegans* as an *in vivo* model to systematically evaluate the protective effects of capsaicin against cold stress and to elucidate the underlying molecular mechanisms. Our results demonstrate that capsaicin treatment significantly improves neuromuscular function and metabolic activity under mild cold conditions (4 °C), accelerates locomotor recovery following acute cold shock (−20 °C), and enhances adaptive memory upon repeated cold exposure. Furthermore, capsaicin reduces intestinal lipofuscin accumulation, a hallmark of oxidative damage, indicating its antioxidant capacity.

Through bioinformatics analysis and molecular docking, we identified STAT3 as a potential core target mediating the cryoprotective effects of capsaicin. These findings reveal a previously unrecognized function of capsaicin as a cryoprotective agent and provide mechanistic insights into its action. This study not only expands the pharmacological profile of capsaicin but also establishes a foundation for its potential application in the prevention and treatment of cold stress-related disorders.



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sciforum-166614: Exploring the Energetic Contributions of Halogen Atoms to Protein-Ligand Interactions

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Halogen atoms are highly valued in drug discovery due to their lipophilicity and their potential to form halogen bond (XB) interactions. However, the limited understanding of the factors that govern the formation of favorable XBs in protein-ligand interactions highlights the need for a thorough investigation of their structural and energetic properties. In addition, with the development of various computational tools for designing favorable XBs during lead optimization, a systematic benchmarking of these methods for calculating halogen interaction energies in protein-ligand complexes is essential. In this study, we constructed a data set of protein-ligand complex structures featuring halogen interactions and evaluated the performance of molecular mechanics (MM) and quantum mechanics (QM) methods in predicting the relative binding affinity. QM achieved the best performance, with Pearson correlation coefficient of 0.921 for XB systems and 0.667 for hydrophobic interaction systems. In contrast, MM methods were less effective because of inaccuracies in XB energy terms and their failure to account for polarization and induction effects. We also performed a detailed analysis of factors affecting performance, including ligand binding poses in pocket microenvironments, desolvation effects, and the complex energy components and electron distributions associated with halogen atoms. By integrating MM and QM methods, we developed an efficient structure-based XB 'design in' workflow for lead optimization. The practical value of this workflow was demonstrated by designing XB interactions in kinase targets.



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sciforum-167174: Molecular Physicochemical Property Prediction Method based on Structure and Characteristics

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The prediction of molecular physicochemical properties—such as solubility, hydration free energy, and lipophilicity—plays a crucial role in multiple fields, including drug discovery and materials science. Current prediction methods predominantly fall into two categories: machine learning methods based on molecular descriptors and deep learning methods that learn representations directly from molecular structures. However, when evaluated under rigorous scaffold splitting, these methods often exhibit limited generalization capability, resulting in unsatisfactory prediction accuracy. In this study, a method named MSCMP is proposed to predict the physicochemical properties of molecules, which effectively utilizes the enhanced graph representations capturing molecular motifs and the optimized selection of pharmacophore and physicochemical characteristics. The use of the molecule structure extract model and the fusion strategy of molecule structure and characteristics significantly improved the prediction performance. Experimental results demonstrate that MSCMP achieves superior predictive accuracy, with lower Root Mean Square Error (RMSE) scores on three benchmark datasets: 0.787 (ESOL), 1.875 (FreeSolv), and 0.615 (Lipophilicity). These results outperform six state-of-the-art methods, including D-MPNN, G-Motif, MGSSL, MolCLR, KANO, and HiMol. Furthermore, our analysis reveals that robust prediction relies not only on molecular graph and motif representations but also on key pharmacophore and physicochemical characteristics—such as hydrophobic group count and LogP—which show strong correlations with the target molecular properties.



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sciforum-177809: Multifunctional Stimuli-Responsive Nanomicelles for the Targeted Delivery of Chloroethylnitrosoureas: A Strategy to Overcome Chemoresistance

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The clinical efficacy of carmustine (BCNU) and other chloroethylnitrosoureas (CENUs) is significantly hampered by poor tumor selectivity, dose-limiting toxicity, and drug resistance mediated by O⁶-alkylguanine-DNA alkyltransferase (AGT). To address these challenges, we have developed a series of multifunctional, stimuli-responsive nanomicelles designed for the targeted delivery of BCNU and the simultaneous inhibition of AGT. Our platform leverages the tumor microenvironment (TME) to achieve controlled drug release and enhanced therapeutic index. The nanocarriers are constructed from biocompatible polysaccharides, such as hyaluronic acid (HA) and carboxymethyl chitosan (CMCS), which provide active tumor targeting via CD44 or folate receptor engagement. A key design feature is the covalent conjugation of an O⁶-benzylguanine (BG) AGT inhibitor through a hypoxia-sensitive azobenzene linker, sometimes in combination with an esterase-cleavable bond for dual responsiveness. This architecture ensures that the AGT inhibitor and BCNU are released specifically within hypoxic tumor tissue. In vitro studies confirmed hypoxia- and/or pH-selective cytotoxicity against various cancer cell lines, with IC₅₀ values significantly lower than those for free BCNU, particularly in AGT-overexpressing cells. For glioma therapy, the micelles were further functionalized with Tween-80 to facilitate blood-brain barrier (BBB) penetration, demonstrating enhanced transport across in vitro BBB models. In vivo, these nanomicelles showed preferential accumulation at tumor sites, potent antitumor efficacy, and reduced systemic toxicity. This integrated strategy of active targeting, TME-triggered release, and AGT inhibition offers a promising and versatile platform to revitalize CENU-based chemotherapy.



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sciforum-167614: Small molecules reveal molecular mechanisms of SARM1 activation and inhibition

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Nicotinamide adenine dinucleotide (NAD⁺) is a ubiquitous biomolecule essential for cellular life. Beyond its role in redox metabolism, NAD⁺ serves as a substrate for diverse enzymes in NAD⁺-dependent signaling pathways, including NAD⁺ glycohydrolases. We have recently discovered the NAD⁺-glycohydrolysing activities of proteins with Toll/interleukin-1 resistance/receptor (TIR) domains, including Sterile alpha and TIR motif containing 1 (SARM1), a promising target against axon degeneration.

Our work demonstrated that nicotinamide mononucleotide (NMN), a key NAD⁺ precursor, competes with NAD⁺ to bind SARM1 allosterically, triggering cross-domain conformational changes that switch SARM1 into an active enzymatic state. In addition, we uncovered a base-exchange mechanism that enables the in situ generation of potent SARM1 inhibitors from small-molecule fragments, revealing an unexpected route for orthosteric inhibition at the active site. Using the activator NMN with a representative base-exchange inhibitor, we revealed the molecular mechanisms underlying allosteric activation and orthosteric inhibition of SARM1.

Together, these findings establish small molecules as powerful probes to dissect SARM1 regulation. They provide a mechanistic framework to guide the rational design of both allosteric modulators and orthosteric inhibitors for therapeutic intervention, particularly in light of recent developments and mixed outcomes in the discovery of a growing number of base-exchange inhibitors against SARM1.



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sciforum-162559: A family of compounds highly potent against *Plasmodium* and *Leishmania* with a novel mechanism of action targeting protein condensates

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Introduction

The scarcity of antimalarial drugs in use and the constant evolution by the parasites of resistance to all of them call for the urgent discovery of new compounds whose ideal characteristics include: (i) belonging to a new chemical family with no other antiparasitic drugs described, (ii) highly potent against *Plasmodium* (IC₅₀ 100 nM), (iii) having a selectivity index above 1000, (iv) having a rapid, simple and cost-efficient synthesis and a long shelf life, (v) with multiple targets in the pathogen, (vi) being irresistible and (viii) fast-acting, with (ix) multi-stage and (x) multi-species activity, (xi) being long-acting injectables and (xii) with a novel mechanism of action.

Methods

We have used (1) chemical synthesis to obtain a novel class of compounds complying with the above characteristics, which were designed by systematic modification of different parts of the structure of the hit YAT2150, (2) *Plasmodium falciparum*, *Leishmania infantum* and *Saccharomyces cerevisiae* cultures to investigate the effects on them of the synthesized derivatives, and (3) fluorescence confocal microscopy to characterize their antiparasitic mechanism of action. Cellular thermal shift assays are being used to identify in the malaria and leishmaniasis parasites the protein targets of this family of compounds.

Results

We report that the YAT2150 family of analogs includes highly potent compounds against *P. falciparum* and *L. infantum*. Within the synthesized derivatives, we have identified novel molecules which bind to biomolecular condensates in living cells from the malaria and leishmaniasis parasites and in a yeast model. *P. falciparum* and *L. infantum* cells treated with these molecules displayed puncta formations, which rapidly dissolved upon treatment with 1,6-hexanediol, a known disruptor of phase-separated condensates.

Conclusions

These findings suggest the existence of functional condensate-like structures in the malaria and leishmaniasis parasites, and hint at conserved mechanisms of phase separation that may be exploitable for therapeutic targeting.



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sciforum-159067: Atomistic Insights into Carbohydrate Recognition by the Fungal Chitin-Binding Therapeutic Monoclonal Antibody CC5

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The chitin-specific monoclonal antibody (mAb) against the pathogenic fungus *Cryptococcus neoformans*, designated “mAbCC5,” has been generated and experimentally demonstrated to play a critical role in controlling cryptococcosis. Furthermore, the complementarity-determining regions (CDRs), which constitute the key structural elements responsible for antigen recognition, have been documented. However, the atomistic basis of antigen binding remains unexplored. Here, we aim to define these interactions at structural and atomic resolution. The 3D structure of mAbCC5 was first generated using AlphaFold3 in combination with the PDB template of available antibody, followed by structural refinement and validation. Protein–glycan docking was then performed using HADDOCK3, incorporating experimentally informed interaction restraints to identify plausible binding poses and key recognition residues. The most favorable docked complexes between chitopentose and mAbCC5 were subjected to three independent 1 μ s all-atom molecular dynamics (MD) simulations in explicit solvent to assess conformational stability and dynamic behavior of the mAbCC5–glycan complex. To quantify binding energetics, molecular mechanics MM-GBSA and quantum mechanics FMO calculations at RIMP2/6–31G* level with PCM solvation were carried out, providing estimates of the binding free energy and residue-level energetic contributions. The combined results highlight key CDR residues involved in fungal chitin recognition and underscore the importance of electrostatic and van der Waals interactions in stabilizing the complex. FMO calculations indicated that only four monomers interacted with the CDRs, accounting for 54.69, 28.27, 9.74, and 7.40% of the total interaction energy, respectively. This finding emphasizes that only four monomers are crucial for binding. Per-residue energy decomposition analysis and PIEDA suggest that more than 65% of the total interaction energy is contributed by the heavy chain. Additionally, three arginine residues act as key hotspots for carbohydrate recognition. Overall, this study provides atomistic insights into mAbCC5–chitin recognition for antibody optimization and experimental validation, supporting the development of universal antifungal therapeutic antibodies.



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sciforum-166610: Cyclic Imides as Phosphodiesterase 4 Inhibitors in the Management of Psoriasis

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Psoriasis is a chronic inflammatory skin disorder for which effective oral options remain limited. PDE4B has gained attention as a therapeutic target because it modulates inflammatory pathways and offers a more favorable safety profile compared to non-selective PDE4 inhibitors. Herein, we report a new class of cyclic imide derivatives as selective PDE4B inhibitors for the potential treatment of psoriasis. Among the synthesized derivatives, compounds **1a**, **2g**, and **2k** showed promising PDE4B inhibition (>50%, 1 μ M) *in vitro*, with IC₅₀ values of 0.493, 3.997, and 0.226 μ M, respectively. Notably, the hit **2k** exhibited clear selectivity towards PDE4B over PDE4D *in silico*. Molecular docking, MD simulation, DFT and binding free energy calculations further supported the superior *in vitro* activity of **2k** over **1a** and **2g**. Docking analyses indicated that **2k** selectively engages the CR3 region of PDE4B through key interactions with LEU-674 and LYS-677. Additional stabilizing interactions with catalytic residues GLN443 and PHE446, as well as coordination with the Zn²⁺ and Mg²⁺ ions, were also observed. MD simulations performed over 100 ns demonstrated greater complex stability for PDE4B compared to PDE4D, reflected by lower RMSD and Rg values. The compound **2k** was therefore identified as an initial hit and was pursued for further studies. Furthermore, **2k** significantly reduced the induction of TNF- α in HEK293 cells, indicating anti-inflammatory potential with IC₅₀ of 3.39 μ M. Collectively, the compound's selective PDE4B engagement *in silico* along with *in vitro* PDE4B inhibition and anti-inflammatory activity, highlight **2k** as a promising hit molecule for further optimization.



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sciforum-167482: Development of a high-throughput screening protocol for studying tumor cell migration

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The scratch assay is a well-established technique for measuring cell migration and proliferation under *in vitro* conditions. Traditionally, a pipette tip is used to manually create a scratch on confluent cell cultures, followed by imaging. The removal of cells induces cell migration into the open area. Migration activity is determined by comparing the width of the scratch at baseline and after incubation. This method is used to evaluate the effects of various treatments on cell migration. However, its use with large sample numbers is limited by the inhomogeneity of manual scratches and the need to use a large diameter vessel, which requires the use of large sample volumes. Furthermore, inconsistent cell migration can set back precise measurement. In response to these limits, we set out to develop a more precise and automated, low volume method which automatizes both scratching and imaging. Our method allows the creation of scratches of uniform size and position on cell cultures distributed across 96-well microplates using a Tecan Freedom EVO liquid handling robot without any special upgrade. This advancement reduces sample volume and simplifies application to larger sample numbers. Measurement and analysis of migration activity were also enhanced; both image acquisition and analysis were automated using a Perkin Elmer Opera Phenix High-Content Analyzer. Machine learning was used to recognize large, open areas, allowing precise quantification of migratory activity. The optimized method was validated using U2OS osteosarcoma cell lines and performing a trial screening with a library of 80 compounds. Our work was supported by NKFIH K 147482.



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sciforum-178036: Discovery of a Novel PDK1-Targeting PROTAC by Disrupting Its Non-Enzymatic Functions for Breast Cancer Treatment

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Introduction

3-Phosphoinositide Dependent Kinase-1 (PDK1) plays a critical role in the progression of breast cancer. However, the clinical potential of traditional PDK1 inhibitors is hampered by poor target selectivity and low inhibitory potency. This study aims to leverage Proteolysis Targeting Chimera (PROTAC) technology to develop novel PDK1 degraders that offer high selectivity and the ability to disrupt non-enzymatic functions.

Methods

A series of PDK1 PROTACs was designed and synthesized. Biological activity was evaluated in MDA-MB-231 and MCF-7 cells. Cell viability, proliferation, and apoptosis were assessed by CCK-8, colony formation, and flow cytometry, and PDK1 degradation was examined by Western blotting. RT-qPCR was performed to assess the effect of the PROTAC on PDK1 mRNA levels. Selectivity was profiled by proteomics, and downstream pathways were analyzed by RNA-seq comparing PROTAC versus inhibitor. PDK1-interacting proteins were identified by IP-MS and Co-IP. In vivo efficacy and safety were evaluated in a nude mouse xenograft model.

Results

Compared with the inhibitor GSK2334470, the candidate compound **48** exhibited superior anti-proliferative activity, significantly suppressed colony formation, and induced stronger apoptosis. Proteomics confirmed high selectivity for PDK1, and competition assays verified proteasome-dependent degradation. In a breast cancer xenograft model, it demonstrated potent anti-tumor efficacy with good tolerability. RNA-seq revealed that its anti-tumor activity may involve regulation of PDZK1IP1, suggesting engagement of non-enzymatic functions distinct from small-molecule inhibition.

Conclusions

In summary, this study developed a novel PDK1-PROTAC with potent degradation and anti-proliferative activity in breast cancer cells. It uncovered a distinct anti-tumor mechanism beyond conventional inhibition, offering a promising therapeutic strategy for breast cancer and other malignancies.



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sciforum-176391: Electrochemical Peptide Modification Toward Pharmaceutical Applications

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Peptide- and protein-based drugs show great promise in antitumor, immunomodulation and other therapeutic fields due to their high affinity, strong specificity and excellent safety, with steady growth in the global market. However, their clinical translation is severely hindered by poor molecular stability, short in vivo half-life and high clearance rate. Chemical modification is a key approach to improve pharmacokinetic properties and druggability, yet traditional strategies suffer from inherent limitations including limited reaction modes, harsh conditions, poor site selectivity and low biocompatibility. As a green and efficient method, electrosynthesis uses electrons as clean reagents and enables site-specific peptide modification under mild conditions via precise regulation of electrode potential, offering a novel strategy for the precise modification of sensitive biomacromolecules. Thus, developing novel pharmaceutically oriented electrochemical peptide modification strategies with high selectivity and good biocompatibility is crucial for advancing peptide drug innovation and clinical translation. Our group has established site-selective modification and labeling methods for linear peptides via electrosynthesis, including the synthesis of peptide aldehydes and peptide alcohols, as well as the diazidation labeling of dehydroalanine. Through the formation of N-S bonds, we developed synthetic strategies for stapled peptides and cyclic peptides, such as tryptophan-containing cyclic peptides. Additionally, by introducing selenium, we constructed selenium-containing functional peptides and selenium-containing lead compounds, and identified the first selenated isoquinoline inhibitor of DDX10 helicase, which exhibits significant anti-lung cancer activity. These studies provide new insights into the design of active molecules and candidate lead compounds for disease treatment.



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sciforum-165268: G3BP1/2-Targeting PROTAC Disrupts Stress Granules Dependent ATF4 Migracytosis as Cancer Therapy

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Stress granules (SGs) are membraneless cytoplasmic compartments that form in response to stress stimuli. In these compartments, most translation factors stall, except for activating transcription factor 4 (ATF4), which is preferentially translated to ensure cell survival under stressful conditions. Cancer cells encounter various stress conditions in the tumor microenvironment during tumorigenesis; however, how they exploit the pro-survival effects of ATF4 in SGs remains unclear. G3BP1/2 are central nodes of the SG network, regulating SG dynamics. In this study, we designed two small molecules, #129 and PROTAC (Proteolysis Targeting Chimera) degrader 129 (PT-129), which specifically target the NTF2L domain of G3BP1/2, a crucial hub for protein and RNA interactions. These compounds inhibit the formation of stress granules in stressed cells and disassemble pre-existing stress granules. Furthermore, pharmacological inhibition by PT-129 suppressed fibroblast-mediated cancer cell growth in vitro and reduced tumor growth in vivo. Mechanistically, SG facilitates the delivery of ATF4 from fibroblasts to tumor cells via migracytosis, a primary mediator of fibroblast-associated tumor growth. PT-129-mediated disassembly of stress granules disrupts ATF4 delivery, thereby preventing cancer cell proliferation. These compounds, therefore, represent powerful tools for gaining molecular insights into SGs and hold promise for cancer therapeutic interventions by modulating stress granule dynamics.



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sciforum-167111: Investigating the Impact of Bridge Ring Moieties on Kinase Inhibitor Selectivity

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Introduction

Developing highly selective inhibitors remains a significant challenge in kinase chemical biology due to the highly conserved ATP-binding pockets, which often lead to off-target toxicity. Incorporating bridge ring moieties has emerged as a promising strategy to enhance selectivity. However, the molecular mechanism by which these rigid cyclic scaffolds confer selectivity remains poorly understood, hindering the rational design of kinase inhibitors.

Methods

To elucidate the molecular basis of this selectivity, we performed comprehensive thermodynamic and kinetic analyses on A397, a representative kinase inhibitor featuring a bridge ring moiety, in complex with the JAK family kinases. Our approach integrated molecular dynamics simulations with binding free energy decomposition and steered MD to evaluate the energetic contributions of individual residues.

Results

The selectivity mediated by the bridge ring moiety stems from differential structural cooperation between the ligand and protein motifs, which in turn alters the energetic contributions of key residues. We identified key binding residues and demonstrated the P-loop's critical contribution to selectivity. The bridge ring moiety has a lower probability of achieving perfect shape and electrostatic complementarity with off-target kinases, thereby enhancing selectivity through structural mismatch in non-target pockets.

Conclusion

This study provides mechanistic insights into the binding of A397 with the JAK family, highlighting the role of the P-loop in mediating selectivity. These insights offer a robust framework for utilizing bridge ring moieties in the rational design of highly selective kinase inhibitors, potentially expanding the accessible chemical space for highly targeted drug discovery.



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sciforum-169897: Phagocytosis-Stimulating Activity of Thick Extracts of *Dracocephalum ruyschiana* L. Growing in Central Kazakhstan

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Introduction

Plants of the genus *Dracocephalum* L. are known for their high content of biologically active compounds with anti-inflammatory, antioxidant, and immunomodulatory properties. This study focuses on *Dracocephalum ruyschiana* L., found in Central Kazakhstan, which has not been thoroughly examined for its phytochemical composition and pharmacological effects. Considering the rising incidence of health issues related to impaired innate immunity, the research aims to determine the phagocytosis-stimulating activity of thick extracts from *D. ruyschiana* L.

Methods

Methodology involved using an ultrasound-assisted extraction method for the extract from the aerial parts. The reference drug “Immunorm” (8% alcoholic juice of *Echinacea purpurea*, Germany) was employed for comparison. The phagocytic activity of neutrophils from a healthy donor was assessed using a method by Galankin V.N., with *Staphylococcus aureus* (ATCC 6538) as the target.

Results

The 70% *Dracocephalum ruyschiana* L. extract significantly enhanced neutrophil phagocytosis compared with the control, increasing the phagocytic index to $54.1 \pm 1.8\%$ and the phagocytic number to 11.4 ± 2.7 , which exceeded the control value by 52% ($p < 0.05$). The phagocytosis-stimulating activity of the extract was comparable to that of the reference drug *Immunorm*, indicating a pronounced stimulatory effect on the functional activity of peripheral blood neutrophils and confirming its immunomodulatory potential.

Conclusions

The *Dracocephalum ruyschiana* L. extract (70%) exhibited pronounced phagocytosis-stimulating activity, increasing both the phagocytic index and the phagocytic number of peripheral blood neutrophils. It was found that the stimulatory effect of the extract on neutrophil functional activity is comparable to that of the reference drug “Immunorm.”



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sciforum-171424: Pharmacological Activation of NAD⁺ Biosynthesis for Neuroprotection

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Nicotinamide adenine dinucleotide (NAD⁺) is a central metabolic coenzyme and signaling molecule essential for cellular energy homeostasis, stress responses, and cell survival. Declining NAD⁺ levels are implicated in aging and a wide range of human diseases, including neurodegenerative disorders and peripheral neuropathies. However, pharmacological strategies that restore NAD⁺ through direct activation of its biosynthetic machinery remain limited. Here, we report the discovery and characterization of small-molecule activators targeting key enzymes in NAD⁺ biosynthetic pathways, including nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide mononucleotide adenylyltransferases (NMNATs). Target-based high-throughput screening identified multiple chemotypes that robustly enhance enzymatic activity. Structural analysis and computational modeling of enzyme-activator complexes revealed previously unrecognized allosteric mechanisms that stabilize catalytically favorable conformations. Cellular studies demonstrated that these activators markedly elevate intracellular NAD⁺ levels, driving metabolic and transcriptional reprogramming consistent with enhanced stress resilience. Importantly, optimized lead compounds exhibited strong neuroprotective efficacy in a mouse model of chemotherapy-induced peripheral neuropathy (CIPN), preserving axonal integrity and sensory function. In parallel, we investigated the regulation of NAD⁺ biosynthesis under energetic stress, uncovering metabolic control mechanisms that further inform therapeutic targeting. Together, these findings establish allosteric activation of NAD⁺ biosynthetic enzymes as a viable strategy to counteract NAD⁺ depletion and associated neurodegeneration. These compounds represent promising candidates for the treatment of neurological and metabolic disorders driven by impaired NAD⁺ homeostasis.



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sciforum-166975: Photodynamic Inactivation of *Salmonella typhimurium* in Fruit Juice Using Erythrosin B

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Introduction

Fruit juice provides a conducive environment for bacterial growth because it lacks the natural defence barriers, such as the fruit peel and cell walls, which increases the risk of contamination. Pathogens like *Salmonella typhimurium* are known to survive in acidic environments, including orange juice. Therefore, effective control methods are needed to prevent microbial contamination of juice. The application of photodynamic inactivation (PDI) has been proposed as an effective microbial control strategy. The PDI is based on the combination of three components: a light source, a photosensitizer, and molecular oxygen, leading to the generation of reactive oxygen species (ROS) that cause irreversible microbial cell damage. Several photosensitizers have been studied, and erythrosine B is a candidate for further development. The purpose of the research was to evaluate the potency of erythrosine B as a photosensitizer in PDI to solve this problem.

Methods

The experimental design used three groups to test the effectiveness of PDI: samples treated with erythrosine B alone (+E-L, dark toxicity control), samples treated with green light alone (-E+L, erythrosine B control), and samples treated with erythrosine B and green light (+E+L, PDI treatment). We observed the treatment in three time exposures (10, 20, and 30 minutes).

Results

An increase in bacterial counts was observed in the control group following treatment. In contrast, the PDI treatment group demonstrated a reduction in bacterial counts, with the greatest effect observed after 30 minutes of irradiation, resulting in up to 69.2% reduction.

Conclusions

PDI with photosensitizer erythrosine B has the potential to be developed to overcome *Salmonella typhimurium* bacterial contamination in juice.



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sciforum-167436: Reagent-DOCK: Enabling Ultra-Large-Scale Docking Through Divide and Conquer

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Drug-like compounds occupy an immense chemical space, making exhaustive exploration computationally prohibitive. Because viable drug candidates are more likely to emerge from larger compound libraries, substantial efforts have been devoted to expanding and exploring this space. The rapid growth of accessible chemical space further underscores the need for ultra-large-scale virtual screening. As a central technique in virtual screening, molecular docking is fundamentally challenged by the curse of dimensionality when confronted with extremely large chemical and conformational spaces. To address this issue, we adopted a divide-and-conquer strategy and developed a workflow termed Reagent-DOCK. Instead of operating on intact molecules as in traditional approaches, our method prepares, samples, and docks molecular fragments and subsequently reassembles them. A primary application of Reagent-DOCK is the virtual screening of building blocks or reagents, which can substantially reduce the search effort in both conformational and chemical space. We first evaluated Reagent-DOCK using more than 800 experimental complex structures in a redocking benchmark, achieving a 63% reproduction rate of experimental poses. We then collected approximately 1,300 modeled or experimental structures of the sEH target bound to urea-containing compounds with reported activities for cross-docking evaluation, in which Reagent-DOCK successfully reproduced 40% of the poses. Finally, we conducted a retrospective virtual screen on the sEH target using over 28 million make-on-demand urea-containing compounds derived from the Enamine amine and isocyanate libraries. Reagent-DOCK delivered performance comparable to traditional docking approaches while reducing computational cost by several orders of magnitude. Overall, our benchmark results highlight the strong potential of Reagent-DOCK for ultra-large-scale docking across vast chemical spaces.



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sciforum-166555: Study of the anti-inflammatory activity of *Ferula songarica* herb under systemic administration

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Introduction

The aerial parts and roots of *Ferula songarica* contain a complex of biologically active compounds that have been reported to exhibit anti-inflammatory, antioxidant, and antimicrobial activities. Herbal preparations based on *Ferula songarica* are considered a promising approach for the treatment of inflammatory processes of various etiologies.

Methods

The study was conducted on 160 white male mice aged 2 months with an average body weight of 20–21 g under intragastric administration. Acute inflammatory reaction was induced by sub-plantar injection of 0.1 mL of a 2% formalin solution. The studied phytopreparations were administered by forced gavage daily for one week. Paw edema was assessed by measuring the difference in paw diameter using a caliper at 4 and 24 hours after inflammation induction compared to the paw diameter before induction. The reference drug (diclofenac sodium) was administered intraperitoneally at a dose of 10 mg/kg 1 hour prior to edema modeling. The anti-inflammatory effect was evaluated by the reduction in paw edema in animals receiving the studied herbal preparations relative to the control group.

Results

Systemic administration of *Ferula songarica* phytopreparations in male mice using an acute formalin-induced edema model demonstrated the presence of anti-inflammatory activity. The effect was manifested as a reduction in paw edema, while the preparations were well tolerated by the animals and did not cause adverse effects upon systemic administration.

Conclusions

As a result of the study, it was established that all investigated phytopreparations exhibited anti-inflammatory effects when administered for one week. The essential oil and ethanolic extracts of *Ferula songarica* prevented the development of edema within the first 4 hours at a level comparable to the reference drug, diclofenac sodium. After 24 hours, edema was less pronounced in all groups receiving the plant-derived preparations compared to the control group. Thus, it can be concluded that the studied objects demonstrate a pronounced anti-inflammatory effect.



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sciforum-178064: Targeted Degradation of Prolyl Hydroxylase Domain Enzyme 1/2 (PHD1/2) as a Novel Therapeutic Strategy for Acetaminophen-Induced Acute Liver Injury

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Introduction

Acute liver injury (ALI) is a severe clinical syndrome leading to substantial morbidity and mortality worldwide, and there is no effective treatment in clinical practice. Prolyl hydroxylase domain enzyme 1/2 (PHD1/2) is a key regulator of hypoxic adaptation and metabolic homeostasis, representing a promising therapeutic target for tissue damage and repair.

Methods

We designed and synthesized a series of proteolysis-targeting chimeras (PROTAC), which were then screened against MDA-MB-231 cells to identify initial hits. **SH-26** was selected for further characterization and mechanism studies. The hepatoprotective effect of **SH-26** was validated in both *in vivo* and *in vitro* models of APAP-induced acute liver injury using Western blotting, cell viability assays, confocal microscopy, immunohistochemistry, H&E staining, and quantitative real-time PCR.

Results

We developed novel PHD1/2 degraders using PROTAC technology. Our lead compound, **SH-26**, a cereblon (CRBN)-recruiting PROTAC, induced PHD1/2 degradation in a concentration-, time-, and ubiquitin-proteasome system (UPS)-dependent manner across multiple cell lines. In an acetaminophen (APAP)-induced acute liver injury (ALI) model, **SH-26** demonstrated significant hepatoprotective effects, attenuating hepatic inflammation and necrosis without detectable cytotoxicity. Mechanistically, **SH-26**-mediated PHD1/2 degradation attenuated APAP-triggered reactive oxygen species (ROS) accumulation, mitochondrial dysfunction, and NLRP3 inflammasome activation, leading to robust *in vivo* protection against ALI through concurrent suppression of inflammation and inhibition of the mitochondrial apoptotic pathway.

Conclusion

In summary, this work validates targeted PHD1/2 degradation as a promising therapeutic strategy, establishes **SH-26** and its negative control **28** as essential chemical tools for probing PHD1/2 biology, and positions **SH-26** as a promising therapeutic candidate for APAP induced ALI and other PHD1/2-dysregulated diseases.



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Session 2. Medicinal Chemistry Tales

sciforum-177993: Discovery of Novel Selective JNK3 Inhibitors via Scaffold Hopping and Structure-Based Optimization: From Pan-JNK Inhibitor CC-930 to Brain-Penetrant Neuroprotective Candidate YY24

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Introduction

c-Jun N-terminal kinase 3 (JNK3) is a promising target for Alzheimer's disease (AD) due to its brain-specific expression and role in neuronal apoptosis. However, achieving high selectivity over JNK1/2 isoforms remains challenging. The pan-JNK inhibitor CC-930 exhibits potent JNK3 inhibition ($IC_{50} = 6$ nM) but lacks isoform selectivity. This study aims to discover novel selective JNK3 inhibitors with favorable drug-like properties through scaffold hopping and structure-based optimization of CC-930.

Methods

A series of 6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine derivatives were designed and synthesized. Inhibitory activities against JNK isoforms were evaluated using ADP-Glo assays. Molecular docking and 500 ns molecular dynamics simulations were conducted to elucidate binding modes. Neuroprotective effects against $A\beta_{25-35}$ -induced cytotoxicity in SH-SY5Y cells were assessed. In vitro metabolic stability was evaluated in human liver microsomes, and in vivo pharmacokinetic properties of YY24 were characterized in rats following oral administration (10 mg/kg).

Results

Introducing bicyclic aromatic acyl groups into the deep hydrophobic pocket significantly enhanced both potency and JNK1/2 selectivity. The optimal compound YY24 (JNK3 $IC_{50} = 7.6$ nM) demonstrated comparable potency to CC-930 with markedly improved selectivity. MD simulations revealed YY24 forms a stable cation- π interaction with Lys93, explaining its superior selectivity. YY24 exhibited significant neuroprotection against $A\beta_{25-35}$ -induced neuronal damage without cytotoxicity. In human liver microsomes, YY24 showed moderate metabolic stability ($t_{1/2} = 31.1$ min). Remarkably, in rat PK studies, YY24 achieved brain penetration with cerebrospinal fluid concentrations of 27.2 and 13.2 ng/mL at 0.25 h and 2 h post-dose, corresponding to plasma concentrations of 619 and 298 ng/mL.

Conclusions

We successfully discovered YY24, a novel selective JNK3 inhibitor with excellent potency, neuroprotection, and desirable brain penetration. This study provides a promising brain-penetrant lead candidate for AD therapeutics and a valuable chemical probe for CNS JNK3 biology.



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sciforum-167067: Aromatic sulfone derivatives as novel potential radioprotective countermeasures

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Ionizing radiation (IR) poses severe health risks, making the development of effective radioprotective strategies an urgent necessity. Radioprotective agents can prevent or mitigate radiation-induced injuries and are among the most effective treatment options.

To date, the FDA has approved various radioprotective agents, including amifostine, palifermin, Prussian blue capsules, and others. However, these agents may have limitations, including suboptimal efficacy, narrow therapeutic windows, and significant side effects such as nausea, rashes and electrolyte disturbances. Therefore, the development of novel effective radioprotective strategies remains urgent.

We synthesized novel bifunctional radioprotectors by coupling aromatic sulfones with nitroxide radicals to achieve enhanced radioprotection through synergistic regulation of oxidative stress and apoptosis pathways. In vitro studies showed compounds 3 and 21 significantly increased HUVECs survival ($\geq 10\%$) under X-ray irradiation. A 3D-QSAR model (CoMSIA, $R^2=0.8239$) revealed that steric matching of para-substituents and the polarity, hydrophobicity, and hydrogen bonding at ortho and meta positions are crucial for activity. Flow cytometry and confocal analysis confirmed that compounds 3 and 21 provided effective radioprotection by reducing radiation-induced apoptosis ($>15\%$) and scavenging intracellular ROS. In vivo, compound 3 significantly improved survival ($\geq 50\%$) in 6 Gy whole-body irradiated BALB/c mice and alleviated multiorgan radiation injury.

In summary, this study has established a new class of radioprotective agents with dual modes of action. The study provides a comprehensive foundation regarding their synthesis, characterization, bioactivity, and preliminary mechanistic insights.



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sciforum-167791: Benzimidazole-Loaded PDA@POM Nanomotors for Combined Photothermal, Catalytic, and Chemotherapeutic Tumor Treatment

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Introduction

Multifunctional nanotherapeutic platforms offer effective strategies for improving tumor selectivity and therapeutic efficacy while minimizing systemic toxicity. Polyoxometalates (POMs) have attracted significant attention as redox-active nanomaterials capable of catalyzing reactive oxygen species (ROS) generation through Fenton-like reactions in the tumor microenvironment. Polydopamine (PDA), with its excellent biocompatibility and strong near-infrared (NIR) absorption, enables efficient photothermal conversion and surface functionalization. In parallel, benzimidazole derivatives are well-established anti-tumor agents, many of which exert their activity through inhibition of β -tubulin polymerization. Integrating these components into a single nanoplatform provides a rational approach for synergistic cancer therapy.

Methods

PDA-functionalized POM nanomotors (PDA@POM) were synthesized and comprehensively characterized by electron microscopy and spectroscopic techniques. Selected benzimidazole derivatives were successfully loaded onto the nanomotors through noncovalent interactions. In vitro studies were performed to evaluate cytotoxicity, intracellular ROS generation, and photothermal performance under NIR irradiation using cancer cell lines. In vivo antitumor efficacy was assessed in BALB/c mice bearing S180 tumors, including tumor growth inhibition, histological examination, and preliminary biosafety evaluation.

Results

The PDA@POM nanomotors exhibited efficient NIR-induced photothermal conversion and pronounced catalytic ROS generation under tumor-relevant conditions. Benzimidazole-loaded nanomotors demonstrated significantly enhanced cytotoxicity compared to free drugs and unloaded nanomotors, indicating a synergistic therapeutic effect. In vivo studies revealed effective tumor accumulation, substantial suppression of tumor growth, and increased intratumoral oxidative stress, while no significant systemic toxicity or damage to major organs was observed.

Conclusions

This study demonstrated that PDA@POM nanomotors loaded with benzimidazole derivatives constitute a powerful multifunctional nanotherapeutic platform. The combination of photothermal therapy, chemodynamic activity, and targeted chemotherapeutic action resulted in enhanced antitumor efficacy, highlighting the potential of this approach for advanced cancer nanomedicine.

Acknowledgements

The financial support of the National Science Fund of Bulgaria, Bulgaria-China Mobility Project KP06-Kitai/6 is gratefully acknowledged.



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sciforum-167796: Chiral Imidazo[2,1-b][1,3,4]thiadiazoles as EGFR-Targeted Anticancer Agents: Synthesis, Biological Evaluation and *In Silico* Studies

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Introduction

Chiral drugs design may offer a significant therapeutic advantage by providing high stereoselectivity towards the target enzyme, enhanced biological activity and improved therapeutic efficacy. The epidermal growth factor receptor (EGFR) remains a validated molecular target in cancer therapy, necessitating the development of novel scaffolds with improved binding affinity and selectivity. The present study aimed to design, synthesize, and biologically evaluate chiral imidazo[2,1-b][1,3,4]thiadiazole derivatives as potential EGFR-targeted anticancer agents.

Methods

The intermediate chiral 2-amino-5-substituted 1,3,4-thiadiazoles were synthesized through cyclization of chiral carboxylic acids with thiosemicarbazide in the presence of phosphorus oxychloride. These intermediates were refluxed in anhydrous ethanol with substituted α -haloketones to yield a series of chiral 2,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazoles. Further structural diversification was achieved via Vilsmeier-Haack formylation and bromination to generate 5-substituted analogues. The preliminary *in vitro* anticancer potential of synthesized compounds was evaluated against Hela cancer cell lines using MTT assay. Molecular docking studies were performed using AutoDock Vina to investigate EGFR binding interactions.

Results

The series of 24 titled compounds were prepared in good yields and characterized by spectral data. 6-Substituted-imidazo[2,1-b][1,3,4]thiadiazole derivatives exhibited cytotoxicity (IC₅₀) in the range of 5.40-55.25 μ M. Nitro and electronegative substituents at 6-phenyl group showed enhanced activity compared to un-substituted analogues. Similarly, 5-bromo and 5-formyl analogues showed enhanced cytotoxicity. Docking studies demonstrated favorable binding affinities toward EGFR, with binding energies in the range of -6.623 to -9.37 kcal/mol exhibiting hydrophilic and hydrophobic interactions with binding acid residues.

Conclusion

The results identify novel chiral imidazo[2,1-b][1,3,4]thiadiazole derivatives as potential EGFR-targeted anticancer agents. The *in vitro* cytotoxicity preliminary results, together with favorable *in silico* binding profiles highlight the potential of this scaffold as a promising lead for further optimization and development.



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sciforum-168496: Design and Synthesis of Platinum(IV)-Based Antitumour Agents Featuring Anti-inflammatory Functionalities

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The oncological utility of conventional platinum(II) chemotherapeutics, such as cisplatin and carboplatin, is frequently compromised by narrow therapeutic windows, severe systemic toxicities, and the emergence of multi-drug resistance (MDR). To address these pharmacological limitations, this study explores the development of novel, dual-action platinum(IV) prodrugs designed to exploit the unique microenvironment of neoplastic tissues. We report the design, synthesis, and characterization of a series of platinum(IV) complexes featuring an octahedral coordination geometry, where the equatorial plane retains the cytotoxic cisplatin scaffold while the axial positions are functionalized with one or two moieties of non-steroidal anti-inflammatory drugs (NSAIDs). These Pt(IV) conjugates are designed to remain kinetically inert in systemic circulation, undergoing intracellular reductive activation to release the active Pt(II) species and the synergistic NSAID ligands. Our findings demonstrate that these complexes exhibit a sophisticated multimodal mechanism of action. By integrating NSAID pharmacophores, the prodrugs achieve significantly enhanced lipophilicity and cellular uptake compared to parent cisplatin. Consequently, these dual-action conjugates represent a significant advancement in the design of next-generation metallodrugs, capable of circumventing resistance pathways while minimizing the adverse effects associated with traditional platinum therapy.

References

1. Stefan Richter, Peter Lönnecke, Dijana Bovan, Nicoleta Andrian, Bianca Stoean, Maria Lehene, Radu Silaghi-Dumitrescu, Luiza Gaina, Sanja Mijatović, Danijela Maksimović-Ivanić, Goran N Ka-luđerović, Evamarie Hey-Hawkins, Dalton Transactions, 54 (2025) 3597-3609. <https://doi.org/10.1039/D4DT03041A>
2. Philipp Fronik, Isabella Poetsch, Alexander Kastner, Theresa Mendrina, Sonja Hager, Katharina Hohenwallner, Hemma Schueffl, Dietmar Herndler-Brandstetter, Gunda Koellensperger, Evelyn Rampler, Joanna Kopecka, Chiara Riganti, Walter Berger, Bernhard K. Keppler, Petra Heffeter, Christian R. Kowol, Journal of Medicinal Chemistry, 64 (2021) 12132-12151. <https://doi.org/10.1021/acs.jmedchem.1c00770>



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sciforum-167723: Design, synthesis, and cytotoxic evaluation of novel hydroxylamine-based squaramides and squaramates

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Introduction

Squaric acid derivatives are the most important members of the oxocarbon acid family, used in medicinal chemistry. Several compounds based on this scaffold have progressed to clinical trials (navarixin), and some are already in therapeutic use (perzifontel, squaric acid dibutyl ester). In this study, we report novel squaramides and squaramates designed to combine two biologically relevant pharmacophores within a single molecule. Substituted hydroxylamines are known to interfere with DNA synthesis and can inhibit metalloproteinases and other enzymes essential for cancer survival and metastasis. In addition, the bis(2-chloroethyl)amine moiety is a well-established alkylating moiety.

Methods

The target compounds were synthesized via a base-catalyzed nucleophilic condensation reaction between squaric acid ethyl ester and the corresponding amines in a two-step process. In the first step, hydroxylamine squaramates were obtained, followed by conversion to hydroxylamine-bis(2-chloroethyl)amine squaramides. Structural characterization was performed using IR, NMR spectroscopy and DFT calculations. Cytotoxic activity was evaluated *in-vitro* against HT-29, A-549, HeLa, MCF-7, HL-60 cancer cell lines, and the non-malignant L929 cell line. Bleomycin and hydroxyurea were used as reference compounds.

Results and Conclusion

The newly synthesized compounds were obtained in good yields (70–80%) and successfully combined two pharmacologically active motifs within a squaric acid-based framework. Infrared spectroscopy reveals characteristic vibrations consistent with related compounds, including two carbonyl stretching bands in the 1800–1650 cm⁻¹ region. DFT studies show that the squaramido hydrogen plays a key role in intermolecular hydrogen bonding. The *in-vitro* assays demonstrate cytotoxic activity in the low micromolar range against both adherent and suspension cancer cell lines, with several compounds displaying potency comparable to bleomycin. Overall, these results prove that the hydroxylamino derivatives of squaric acid to be promising scaffolds for anticancer drug development.

This research was funded by the Bulgarian national science fund, project № КПО6-Китай/6 16.12.2024.



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sciforum-181641: Discovery and Mechanism Study of Novel HBV CpAMs with High Potency and Broad Anti-drug Resistance Activity

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Chronic hepatitis B caused by HBV remains a severe threat to global health. HBV core protein (HBc) is a critical therapeutic target, yet current core protein allosteric modulators (CpAMs) suffer from drug resistance and poor pharmacokinetics. To address these bottlenecks, this study adopted a dual strategy integrating structure-based optimization and hydrophobic tagging (HyT)-mediated degradation to develop next-generation HBc-targeting agents.

First, we combined structure-biology-driven druggable site identification with computational chemistry-guided structural optimization to design novel HBV CpAMs. Pyrrole amide derivatives **21**, **23**, and **24** showed 10- to 100-fold improved potency over the lead GLP-26, and reduced intracellular HBc levels in a dose-dependent manner with a biphasic profile: inhibition at low concentrations and degradation at high concentrations. Co-crystallography revealed that the oxalamide group of **23** formed two new hydrogen bonds with Leu140 in the solvent-exposed region. In HDI mouse model, **23** significantly reduced serum HBV DNA, HBeAg and cccDNA levels, and showed favorable pharmacokinetics ($F=28.7\%$) and potential activity against V124F and R97L mutants.

To further overcome the widespread resistance of clinical HBV mutants, we developed HyT-based HBc degraders, representing the first HyT application in anti-HBV therapy. Representative compound **IIIB-1g**, featuring an adamantyl group, degraded HBc in a concentration- and time-dependent manner *via* the autophagy pathway, and triggered an immune cascade to activate the type I interferon signaling pathway. Notably, **IIIB-1g** effectively degraded 11 drug-resistant mutants, including P25G and T33N that are highly resistant to GLS4. Cellular thermal shift assay, SPR and molecular dynamics simulations revealed the precise binding mode between **IIIB-1g** and HBc. These dual-mechanism molecules not only show potent anti-HBV efficacy and excellent resistance profiles, but also provide a new paradigm for antiviral research targeting viral core proteins.

Collectively, these novel CpAMs exhibit potent anti-HBV efficacy and favorable anti-drug resistance profiles, providing a solid foundation for next-generation anti-HBV therapeutics.



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sciforum-177422: Discovery of a Novel Class of Potent Inhibitors of the m6A Demethylase FTO for the Treatment of Severe CNS Disorders

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The fat mass and obesity-associated protein (FTO) is a non-heme Fe(II)/2-oxoglutarate (2-OG)-dependent dioxygenase that catalyzes the oxidative demethylation of RNA modifications.¹ Abnormal FTO activity appears to be involved in metabolic diseases, multiple cancers, and neuropsychiatric and neurodegenerative disorders.² In the central nervous system, FTO is highly expressed in neurons and regulates dopaminergic signaling, synaptic function, memory, and cognition. Its dysregulation has been associated with impaired neuronal survival and the progression of disorders such as depression and Alzheimer's disease. Very recently, pharmacological inhibition of FTO has been shown to confer neuroprotective effects in preclinical models, supporting its potential as a therapeutic target for severe CNS conditions.^{3,4}

Herein, we report the structure-guided identification of an FTO inhibitor hit and the subsequent hit-to-lead optimization campaign through systematic modification at three parts of the hit molecule. The optimized lead, MGZ-7, exhibits one-digit *in vitro* nanomolar FTO inhibitory potency, which is six-fold higher than that of the reference FTO inhibitor FB23, selectivity over the ALKBH5 demethylase, and favorable DMPK properties (excellent *in vitro* brain permeability, good Caco-2 permeability, low human plasma protein binding, good microsomal stability, and high aqueous solubility) and favorable safety profile (no hERG liability). Thus, MGZ-7 emerges as a promising drug candidate for the treatment of neurodegenerative disorders.

This research was funded by MICIU/AEI/10.13039/501100011033 and ERDF, EU, grant numbers PID2023-147004OB-I00, PID2022-139016OA-I00, and PDC2022-133441-I00.

References

1. Wei, J. et al. Mol. Cell 71, 973-985.e5 (2018).
2. Benak, D., et al. Front. Cell Dev. Biol. 12, (2024).
3. Hu, B. et al. Nat. Commun. 16, 5251 (2025).
4. Irisarri, A. et al. Mol. Med. 31, 73 (2025).



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sciforum-178105: Discovery of Covalent and Non-covalent Isoform-Selective NADPH Oxidase Inhibitors through Ultra-Large Virtual Screening and Medicinal Chemistry Optimization: New Tools for Cancer and Neuroprotection

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Keywords: NADPH oxidase; ROS signaling; ultra-large virtual screening; medicinal chemistry; neuroprotection

Introduction

NADPH oxidases (NOXs) are a unique class of enzymes that generate reactive oxygen species (ROS) as their primary catalytic product. Although physiological ROS signaling is essential for cellular homeostasis, dysregulated NOX activity contributes to several pathological processes, including tumor progression, neuroinflammation, and neurodegeneration. In cancer, NOX-derived ROS sustain oncogenic signaling and metabolic reprogramming, whereas in the central nervous system aberrant activation of NOX isoforms promotes microglial activation and oxidative neuronal damage in disorders such as Parkinson's disease and Alzheimer's disease.¹

Methods

Here we report a medicinal chemistry program aimed at discovering small-molecule NOX inhibitors through structure-based design combined with ultra-large virtual screening of libraries containing hundreds of millions of compounds. A stringent biochemical validation workflow was implemented to eliminate assay-interfering compounds and confirm bona fide NOX inhibition.

Hit scaffolds were advanced through iterative optimization, leading to covalent and non-covalent inhibitors with improved potency and isoform selectivity toward human NOX1, NOX2, NOX4, and NOX5.

Results

Structural modification of the covalent inhibitor VAS2870 produced the first dual NOX2/MAO-B inhibitor, MC4762, which in BV2 microglia markedly reduced ROS production and suppressed proinflammatory cytokines (iNOS, IL-1 β , IL-6).³ In parallel, optimization of initial screening hits generated isoform-selective inhibitors including MC4854 (NOX5), MC4953 (NOX1), and MC4876/MC4921 (NOX2). Notably, MC4876 displayed activity in NOX2-overexpressing cancer cells, and reduced expression of mesenchymal genes and hexokinase-2 in glioblastoma cells.

Conclusions

These results establish new chemical tools to probe NOX-dependent redox signaling and highlight selective NOX inhibition as a promising strategy for both anticancer and neuroprotective drug discovery.

References

1. Bedard K.; Krause K.-H. *Physiol. Rev.* 2007, 87, 245–313.
2. Reis J. et al. *Nat. Chem. Biol.* 2023, 19, 1540–1550.
3. Noce B. et al. *J. Med. Chem.* 2025, 68, 6292–6311.



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sciforum-176292: Functionalizing Thiosemicarbazones for Biomedical Targets

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Thiosemicarbazones (TSC) are a versatile class of molecules with established anti-biological properties. Their medical application is frequently hampered through their pronounced lipophilic character. Approaches towards their applicability are their controlled release from metal complexes, from mesoporous materials, and from polymers, the build-up of TSC-peptide conjugates for their cell-incorporation, and their binding to nanoparticle (NP) surfaces. The advantage of TSC is the vast chemical variability through the four substituents R to R'''. The aim of this broad and ongoing research project is the vast use of TSC as multifunctional units for various purposes.

The approach to use TSC as functional units in conjugates with applications in biomedicine and other fields require the mastering of the chemistry of the TSC, specifically adding groups for anchoring and conjugation. TSC provide the benefit that the formation reaction from carbonyl-containing molecules (bearing R and R') and thiosemicarbazides (bearing R'' and R''') is relatively simple and allows modular synthesis of various derivatives.

The R and R' substitution of TSC was used to introduce further coordinating functions, fluorophores such as anthracenyl, and to enhance the cytotoxicity of TSC by introducing the dipyriddy function. In the N4 position we introduced various conjugating groups such as CN, alkynes, esters, amines, but also anchoring functions such as carboxylates, phosphonates, and thiolates tailored for various nanoparticle surfaces such as SiO₂, Fe₂O₃, TiO₂, Au, and more.

We have worked out strategies to vary all four substituents on TSCs with the aim of providing the necessary chemistry for an extensive use of TSC units in NP conjugates connecting NP to various chemical (e.g. coordinating), physicochemical (e.g. luminescent), and biochemical functions such as cell penetrating peptides or amphiphiles for micelle-formation. Furthermore, TSCs themselves can be useful as both metal-coordinating and cytotoxic entities in such conjugates.



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sciforum-177842: Granulometric Optimization Enhances Phenolic Concentration and Antioxidant Potential of *Abelmoschus esculentus* L. Powder for medicinal Applications.

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Introduction

Okra fruit (*Abelmoschus esculentus* L), known for its high nutritional content, is widely consumed and cultivated in tropical and subtropical regions of the world. It is particularly appreciated by low-income populations, especially in African countries. Despite its benefits, the short post-harvest shelf life poses challenges for local farmers, particularly in regions like Djibouti, characterized by harsh climatic conditions and vulnerability to food insecurity. Okra fruit was processed into powder through lyophilization and milling.

Methods

Five granulometric classes with 160, 220, 500 and 800 μm sieves, as well as the unsieved powder were studied for that purpose. Lyophilized okra fruits were milled and sieved into granulometric fractions (160, 160-220, 220-500, 500-800, and $>800 \mu\text{m}$). Total polyphenol and total flavonoid contents, as well as antioxidant activity, were assessed using Folin-Ciocalteu, DPPH, and ABTS assays.

Results

The finest fraction (160 μm) exhibited the highest TPC ($36.17 \pm 1.1 \text{ mg GAE/g extract}$) and demonstrated the strongest antioxidant activity, with DPPH and ABTS inhibition rates of $89.9 \pm 0.6\%$ and $66.4 \pm 1.4\%$, respectively. In contrast, the highest TFC was observed in the 220-500 μm fraction ($26.94 \pm 0.90 \text{ mg QE/g extract}$), suggesting differential distribution of phenolic subclasses according to particle size. A progressive increase in TPC was observed as particle size decreased. The 160 μm fraction showed significantly higher TPC compared to coarser fractions ($p < 0.05$).

Conclusions

These findings confirm that finer particle sizes enhance the concentration and extractability of bioactive compounds, highlighting the importance of granulometric optimization in the development of functional okra-based powders.



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sciforum-169283: In Vitro Photodynamic Efficacy and Mechanistic Evaluation of Novel Metalloporphyrin Photosensitizers in Ovarian Adenocarcinoma Models

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This comprehensive study details the design, multi-step synthesis, and photodynamic evaluation of a novel series of meso-substituted AB₃-type phenothiazinyl porphyrins and ferrocenylvinyl phenothiazinyl porphyrins. The core macrocyclic framework was initially obtained using the Adler-Longo method, providing a robust scaffold for further chemical modification. Strategic functionalization was subsequently achieved through high-yielding palladium-catalyzed cross-coupling protocols: the AB₃-type derivatives were synthesized via Suzuki-Miyaura coupling, while the more complex ferrocenylvinyl-functionalized variants were prepared through Mizoroki-Heck reactions. These synthesized free-base porphyrins served as indispensable precursors for the coordination of indium(III) and zinc(II) metal centers, resulting in metalloporphyrin complexes with finely tuned electronic and photophysical profiles. The photophysical characterization of these compounds revealed consistent red fluorescence emission in solution, a property that remained unimpaired following cellular internalization within A2780 ovarian cancer cells. Fluorescence microscopy confirmed the stability of these probes in a biological environment, with the In(III) complexes exhibiting superior fluorescence quantum yields ($\Phi_F = 28-30$) compared to their Zn(II) counterparts ($\Phi_F = 10\%$). The therapeutic potential of these agents was evaluated through the measurement of singlet oxygen quantum yields (Φ_Δ) and *in vitro* assays of metabolic activity. The In(III) ferrocenylvinyl-modified analogue (4a) emerged as the most potent photosensitizer, achieving a high Φ_Δ of 0.60 and an IC_{50} 36.38 μ M under light irradiation. Mechanistic studies revealed that treatment with 4a triggers significant intracellular oxidative stress, evidenced by the activation of the Nrf-2 signaling pathway and the upregulation of TNF- α . These results highlight the potential of these complexes as dual-action theranostic tools, combining high-resolution diagnostic imaging with targeted photodynamic intervention for ovarian malignancies.



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sciforum-173133: Niacin-Platinum (IV) complexes, dual action anticancer prodrugs: chemical synthesis and characterization

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Dual action Platinum(IV) prodrugs are a promising class of anticancer agents designed to overcome the side effects of chemically aggressive platinum(II) chemotherapeutics characterized by systemic toxicity. Pt(IV) has a d^6 electronic configuration prompting greater stability and an octahedral geometry. Pt(IV) complexes containing in the equatorial plane four ligands imitating the structure of a Pt(II) chemotherapeutic drug and additional drugs as axial ligands, are most probably inactive until reduced by intracellular antioxidants to the constituent drugs [1,2].

In this work, the novel niacin-platinum(IV) complexes were prepared by the oxidation of cisplatin-type precursors, followed by the coordination of nicotinic acid in the axial positions. The novel niacin-platinum(IV) complexes provide a dual action combining the cytotoxic activity of Pt(II) complexes with the biological role of nicotinic acid as precursor for nicotinamide adenine dinucleotide coenzymes NAD^+ and $NADP^+$ essential for the normal metabolism of carbohydrates, fats and proteins.

The structure of the novel niacin-platinum(IV) complexes was undoubtedly assigned by high-resolution mass spectrometry (HRMS) and NMR spectroscopy. Their redox behaviour was explored by means of cyclic voltammetry.

References

1. Neumann W, Crews B.C., Sárosi M.B., Daniel C.M., Ghebreselasie K., Scholz M.S., Marnett L.J., Hey-Hawkins E., ChemMedChem, 2015, 10(1), 183-192
2. Astner A., Mendrina T., Bachmann F., Berger W., Keppler B.K., Heffter P., Kowol C.R. Chem.Front., 2023, 10. 4126.



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sciforum-177172: Novel 1,2,3,4-tetrahydro-benzo[*h*][1,6]naphthyridine-based hybrids as dual inhibitors of β -amyloid and tau aggregation with anticholinesterase activity

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The structural requirements imposed by the 20 Å-deep catalytic gorge of acetylcholinesterase (AChE) when designing multisite inhibitors that bind at both the catalytic and peripheral aromatic sites of the enzyme have a templating effect that leads to compounds that also fit well in other proteins with pathogenic roles. In this context, we have consistently found that linked hybrids bearing aromatic moieties at both ends of their structures can inhibit protein aggregation [1]. This is the case of the multisite AChE inhibitor DP-128, a 1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-6-chlorotacrine hybrid, a multitarget molecule with potent in vitro anticholinesterase and A β 42 and tau anti-aggregating activity. Indeed, DP-128 inhibits the aggregation of 13 different amyloidogenic proteins and is often used as a reference protein aggregation inhibitor [2]. Here, we present a lead optimization campaign around DP-128, mainly aimed at improving DMPK properties while retaining the potencies on AChE and beta-amyloid and tau aggregation.

Funded by grant PID2023-147004OB-I00 from MICIU/AEI/10.13039/501100011033 and FEDER, EU.

References

1. Luque, F.J.; Muñoz-Torrero, D. Acetylcholinesterase: A versatile template to coin potent modulators of multiple therapeutic targets. *Chem. Res.* 2024, 57, 450–467. <https://doi.org/10.1021/acs.accounts.3c00617>
2. Espargaró, A.; Pont, C.; Gamez, P.; Muñoz-Torrero, D.; Sabate, R. Amyloid pan-inhibitors: One family of compounds to cope with all conformational diseases. *ACS Chem. Neurosci.* 2019, 10, 1311–1317. <https://doi.org/10.1021/acschemneuro.8b00398>



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sciforum-167810: Novel mono- and diamide derivatives of squaric acid: synthesis, *in silico* and *in vitro* biological evaluation

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Introduction

Small molecule therapy is a main strategy for cancer treatment, and squaric acid derivatives have gained attention as valuable drug scaffolds due to their strained aromatic ring, low electron density, and dual hydrogen-bond donor and acceptor properties. A notable example is navarixin, which has successfully completed phase III clinical trials. In this work, we report the synthesis and structural characterization of seven new squaramates and squaramides incorporating five-membered heteroaromatic rings as simplified analogues of navarixin.

Methods

Synthesis was performed using a triethylamine-catalyzed nucleophilic condensation reaction. Structural characterization was done with IR and NMR spectroscopy, DFT calculations, and X-ray diffraction. *In silico* pharmacokinetic profiling was carried out, and cytotoxic activity was evaluated *in-vitro* against the A-549 and MCF-7 cell lines.

Results and Conclusion

Structural analysis revealed several key features. The IR spectrum displays characteristic bands, including a single moderate NH stretching vibration in the 3300–3100 cm⁻¹ region, symmetric and asymmetric carbonyl stretching vibrations between 1800 and 1650 cm⁻¹, and ether stretching band at 1050–1000 cm⁻¹, which allows differentiation between squaramide and squaramate functionalities. DFT calculations show correlate between calculated and experimental vibrational frequencies and identify the energetically favored conformer as the one in which the hydrogen atom is oriented away from the carbonyl groups. X-ray analysis demonstrates that this hydrogen atom is essential for H-bond formation within the crystal structure. Bond lengths obtained from X-ray studies correlate well with those predicted by DFT calculations. *In-silico* pharmacokinetic evaluation indicates favorable drug-like properties, with no violations of Lipinski rule and good predicted GIT absorption. Biological evaluation identified lead compounds with IC₅₀ values of 10.33 and 9.65 μM against A549 cells and 15.74 and 19.46 μM against MCF-7 cells and selectivity indices above 8.

This research was funded by the Bulgarian national science fund, project № КПО6-Китай/6 16.12.2024.



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sciforum-166040: Novel Palladium(II) Complexes Inducing Apoptosis and Cell Cycle Arrest in Breast Cancer Cells

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Introduction

Breast cancer remains one of the most prevalent malignancies worldwide and a major therapeutic challenge due to drug resistance, systemic toxicity, and limited selectivity of current treatments. Although platinum-based drugs such as cisplatin are clinically effective, their severe side effects and rapid development of resistance have prompted the search for alternative metal-based anticancer agents. Palladium(II) complexes have attracted growing interest because of their structural diversity, ligand tunability, and potential to induce cancer cell death through mechanisms distinct from classical platinum drugs. In this study, four newly synthesized palladium(II) complexes were evaluated for their anticancer activity against human breast cancer cell lines.

Methods

The palladium(II) complexes were synthesized via direct C–H ortho-palladation of N-aryl azoles in acetic acid. Cytotoxicity was assessed using the MTT assay in MCF-7 and MDA-MB-231 breast cancer cells, with BEAS-2B normal cells and cisplatin as controls. Mechanistic studies included flow cytometric analysis of cell-cycle distribution and apoptosis, mitochondrial membrane potential ($\Delta\Psi_m$), and activation of initiator caspases-8 and -9.

Results

Among the tested compounds, the most active palladium(II) complex (2a) exhibited the highest cytotoxic potency toward both breast cancer cell lines, surpassing cisplatin, while showing significantly reduced toxicity toward BEAS-2B cells, indicating favorable cancer selectivity. Flow cytometry revealed cell line-dependent cell-cycle arrest, with S-phase accumulation in MCF-7 cells and G₂/M arrest in MDA-MB-231 cells. Apoptosis analysis confirmed a pronounced proapoptotic effect, accompanied by a loss of $\Delta\Psi_m$ and activation of caspases-9 and -8, indicating involvement of both intrinsic and extrinsic apoptotic pathways.

Conclusion

These findings identify the lead palladium(II) complex as a promising candidate for further development of metal-based anticancer agents targeting breast cancer.



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sciforum-177348: One-Pot Synthesis of O-Glycosyl Propargylamine Derivatives as Potential Anticancer Agents

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Glycoside compounds have attracted considerable attention in drug discovery due to their structural diversity, biocompatibility, and favorable pharmacological properties. These characteristics make glycoside-containing molecules particularly valuable in the development of therapeutic agents and biologically active compounds. Propargylamine-containing molecules are also known to exhibit a range of biological activities, including notable anticancer effects, and have therefore been widely investigated as important structural motifs in medicinal chemistry. In this study, we designed and synthesized a series of O-glycosyl propargylamine derivatives to explore their potential as anticancer agents. The design of these molecules was based on the hypothesis that combining glycosyl moieties with propargylamine frameworks could lead to compounds with enhanced biological properties. The target compounds were prepared through a convenient one-pot, two-step synthetic strategy involving sequential glycosylation followed by an A³-coupling reaction under optimized reaction conditions. This approach enabled the efficient synthesis of fifteen O-glycosyl propargylamine derivatives in moderate to excellent yields. In addition, the developed method provides a straightforward, practical, and efficient route for the preparation of structurally diverse glycosylated propargylamine scaffolds, which may be useful for further medicinal chemistry studies and structural modifications. The anticancer activities of the synthesized compounds were evaluated using the MTT cell viability assay against selected human cancer cell lines. Among the tested compounds, five derivatives demonstrated notable cytotoxic activity. Preliminary structure-activity observations suggest that both the glycosyl moiety and substituent effects influence the biological activity of these compounds. These findings indicate that O-glycosyl propargylamine derivatives may serve as promising lead structures for the further development and optimization of new anticancer agents.



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sciforum-165111: Optimization of Halogenated Quinazolinedione Scaffold as Potent and Non-cytotoxic Antimalarial Agents

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The emergence of *Plasmodium falciparum* resistance to artemisinin-based therapies necessitates the urgent discovery of new antimalarials with novel scaffolds and mechanisms. The quinazolinedione scaffold, exemplified by the TCAMS hit TCMD-125133, was identified as a promising, non-cytotoxic starting point. Herein, we report a systematic lead optimization campaign commencing from a simplified and synthetically tractable analogue, compound 9 (IC₅₀ = 586 nM), which was previously reported by our group. A focused library of 57 novel derivatives was designed and synthesized via a concise 5-step route to systematically explore the structure-activity relationships of the terminal phenyl side chain and the quinazolinedione core. Our investigation revealed two critical findings: (i) the 3,4-difluorophenyl side chain was optimal for potency, and (ii) substitution of the core with small, electron-withdrawing halogens was highly beneficial. This strategy led to the discovery of compound 53 which pairs a 6,7-difluoro core with a 3,4-difluorophenyl side chain demonstrating a potent IC₅₀ of 116 nM against *P. falciparum* 3D7. Crucially, this potent analogue and every compound in the series exhibited negligible cytotoxicity against human HepG2 cells (IC₅₀ > 20 µM) indicating a high selectivity. This work validates the 7-halogenated quinazolinedione scaffold as a promising and selective chemotype for further antimalarial drug development. Future efforts will focus on target deconvolution, chiral resolution, *in vivo* pharmacokinetic profiling, and efficacy studies to progress this new antimalarial class.



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sciforum-166764: Phytochemical profiling, antioxidant, and androgenic effects of multi-solvent extracts of *Ziziphus mucronata* on mouse testicular TM3 Leydig cells

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Background

Male infertility is one of the growing health problems in most developing countries however, effective and cheaper treatment methods remain scanty.

Objectives

The study aimed to evaluate the phytochemical profiling, antioxidant content, and androgenic activity of *Ziziphus mucronata* leaf extracts prepared from different solvents.

Methods

Quantitative phytochemical analysis was performed to measure the contents of the polyphenolic compounds. Antioxidant activity was determined using 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and ferric-reducing power (FRAP) assays, while the UPLC-Q-TOF-MS was performed to identify the bioactive metabolites. Cytotoxicity of plant extracts was evaluated *in vitro* on TM3 Leydig cells using CellTiter-Blue cell viability. Moreover, the androgenic activity of extracts was quantified using enzyme-linked immunosorbent assay (ELISA).

Results

The methanolic extract contained the highest total phenolic content (173.04 ± 2.23 mg GAE/g), and ethanolic extract showed the total flavonoid content of 245.52 ± 5.87 mg QE/g, and the acetone extract recorder the proanthocyanidin content of 173.02 ± 0.50 mg CE/g, compared to other extracts. The methanol extract had the highest ABTS scavenging potential (0.48 ± 0.00 μ mol TE/g) the highest DPPH radical scavenging ability (1293.87 ± 2.02 μ mol TE/g) and strong ferric-reducing power (FRAP) activity (0.49 ± 0.00 μ mol TE/g). A total of ten (10) bioactive compounds were identified from the methanolic extract. Additionally, treatment with extracts enhanced testosterone production by TM3 cells in the presence of human chorionic gonadotropin (hCG). Aqueous leaf extracts showed no cytotoxicity.

Conclusions

In conclusion, the fascinating androgenic properties demonstrated by *Z. mucronata* leaf extracts grown in South Africa highlighted their potential natural remedy in sexual health treatment.



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sciforum-169604: Platinum complexes as potential prodrug in cancer therapy

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The design of new multifunctional coordination compounds is intended to overcome the current limitations of platinum-based anticancer drugs, such as side effects, resistance (e.g. via drug efflux transporters) and limited targeting of cellular mechanisms. A series of platinum complexes were synthesised and characterised in terms of their structures and properties using NMR spectroscopy, mass spectrometry, XRD, cyclic voltammetry, UV-Vis spectroscopy and fluorescence spectroscopy. A convenient strategy for the synthesis is to connect bioactive inhibitors possessing one or more hydroxyl groups to platinum(IV) via a carbonate bridge. Inhibitors with carboxyl units are introduced directly as carboxylate ligands. The coordination of the axial ligand through the carbonate or carboxylate units at platinum(IV) (obtained by the oxidation of cisplatin, oxaliplatin, etc.) enables the cleavage of the metal-ligand bonds by intracellular reductants to generate cytotoxic platinum(II) species, along with the release of the bioactive inhibitor. The biological activity of the newly synthesized platinum complexes having the potential to combine two or more drugs in the same pro-drug complex was tested in vitro on the MDA-MB231 breast cancer cells line.

Bibliography

1. Neumann, W.; Crews, B. C.; Marnett, L. J.; Hey-Hawkins, E. Conjugates of Cisplatin and Cyclooxygenase Inhibitors as Potent Antitumor Agents Overcoming Cisplatin Resistance. *ChemMedChem* 2014, **9**(6), 1150–1153. <https://doi.org/10.1002/CMDC.201402074>.
2. Neumann, W.; Crews, B. C.; Sárosi, M. B.; Daniel, C. M.; Ghebreselasie, K.; Scholz, M. S.; Marnett, L. J.; Hey-Hawkins, E. Conjugation of Cisplatin Analogues and Cyclooxygenase Inhibitors to Overcome Cisplatin Resistance. *ChemMedChem* 2015, **10** (1), 183–192. <https://doi.org/10.1002/CMDC.201402353>
3. Li, Z.; Ding, X. J.; Qiao, X.; Liu, X. M.; Xie, C. Z.; Liu, R. P.; Xu, J. Y. Thalidomide-Based Pt(IV) Prodrugs Designed to Exert Synergistic Effect of Immunomodulation and Chemotherapy. *J. Inorg. Biochem.* 2022, **232**, 111842. <https://doi.org/10.1016/J.JINORGBIO.2022.111842>.



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sciforum-177509: PUTTING YOUR COMPOUNDS TO GOOD USE: EU-OPENSREEN's open compound sharing initiative

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Compounds and natural products synthesized by chemists represent a rich, untapped source of novel chemical diversity. In many cases, chemists have limited opportunities to systematically test these compounds against a variety of drug targets. These compounds are also often not readily accessible to the biologists who develop suitable assays. To make the invaluable chemistry of local chemistry groups accessible to a broader scientific community, **EU-OPENSREEN offers chemists the opportunity to make their compounds available**, in a regulated and transparent framework, to a wider community of biologists, who screen these compounds in suitable bioassays. This opportunity allows chemists **to expose their compounds to a range of biological/drug targets to screen for unknown bioactivities**, which would otherwise not be feasible in individual one-to-one-collaborations, thereby **enabling novel collaborations with EU-OPENSREEN users from across Europe and beyond**. The submitted compounds are centrally quality-controlled, stored, and reformatted at the EU-OPENSREEN Central Compound Management Facility in Berlin. Submitted compounds are initially annotated in a suite of cell-based, biochemical and physicochemical assays to analyse their physicochemical and biological properties before being continuously tested and annotated in our screening campaigns. This **'bioprofiling' effort is free of charge to the chemist**, and the **bioactivity data are shared with the respective chemist** who submitted the individual compound. After the initial 'bioprofiling', compounds are tested exclusively at official EU-OPENSREEN partner sites and are not passed on to third parties without consent, so that the chemists retain control over the usage of their compounds.

EU-OPENSREEN is a publicly funded international consortium of approximately 30 academic partner institutes across nine European countries. The consortium supports chemical biologists to implement their drug discovery projects by providing access to high-throughput screening platforms, screening collections and hit-to-lead optimisation support on a collaborative basis.

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sciforum-172898: SB-431542 inhibition of TGF-beta receptor signaling reveals phosphatase-controlled EMT plasticity in lung adenocarcinoma

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Epithelial-mesenchymal transition (EMT) is a dynamic and reversible reprogramming process in which epithelial cells lose cell-cell adhesion and apico-basal polarity and acquire migratory and invasive properties. Beyond its role in development and tissue repair, EMT is now recognized as a central driver of tumor progression, metastatic dissemination and therapy resistance, making it an attractive target space in anticancer drug discovery. EMT is orchestrated by tightly regulated signaling networks, prominently including the TGF-beta pathway. While kinase-driven mechanisms have been extensively studied, the contribution of phosphatase-regulated signaling to EMT control remains insufficiently understood.

TIMAP (PPP1R16B), a regulatory subunit of protein phosphatase 1 and member of the myosin phosphatase family, emerged from in silico analyses as clinically relevant in lung adenocarcinoma. Using stable knockdown models combined with molecular, transcriptomic and functional assays, we show that loss of TIMAP induces a robust EMT phenotype characterized by cadherin switching, activation of SMAD2/3, beta-catenin and Akt signaling, enhanced migration and invasion, metabolic reprogramming and acquisition of stem-like features. Clinically, TIMAP expression is reduced in patient tumors, and low expression correlates with poor outcome, particularly in early-stage disease.

To evaluate the therapeutic tractability of this signaling context, we targeted the TGF-beta type I receptor kinase ALK5 using the small-molecule inhibitor SB-431542. Pharmacological inhibition effectively suppressed SMAD2/3 phosphorylation and attenuated downstream activation of Akt and beta-catenin pathways in TIMAP-deficient cells. Importantly, SB-431542 reduced expression of EMT-inducing transcription factors such as Snail and Slug and restored epithelial marker expression. These findings indicate that the pro-EMT effects driven by TIMAP loss are strongly dependent on TGF-beta receptor activity and can be pharmacologically restrained.



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sciforum-166765: Structure analysis and molecular dynamic processes in the S100B-A β complex under saturation with metal nanoparticles. Application of ^{19}F NMR and HDX mass spectroscopy

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S100B protein plays a dual role in the development of Alzheimer's disease. It protects neurons from degradation at nanomolar concentrations and regulates A β peptide expression and Tau phosphorylation at micromolar concentrations.

Structural analysis of the S100B protein performed by NMR spectroscopy reveals structural alteration under saturation with A β (1-40) or A β (4-40) peptides. Using hydrogen-deuterium exchange mass spectrometry (HDX-MS), we identify regions destabilized during interactions with A β peptides. Those results were supported by ^{15}N and ^{13}C relaxation data, which demonstrate changes in molecular dynamics in the S100B-A β complex.

Metal nanoparticles (Cu, CuO, Zn, ZnO) strongly influence the interaction of S100B with A β peptides, contributing to the development of neurodegenerative diseases. The S100B (F43W) mutant, comprising fluorinated ^{19}F -Trp, was expressed to avoid the effects of the paramagnetic nature of copper and to obtain high-quality fluorescence and ^{19}F NMR data. At the same time, the A β (1-40) and A β (4-40) peptides with ^{19}F -Phe4, located inside the copper-binding ATKUN motif, were synthesized. Taking into account that the ^{19}F resonances in Phe and in Trp residues observed at different chemical shifts, the ^{19}F -NMR provides the unique possibility to extract precise data about S100B – A β complex under saturation with various nanoparticles at different experimental conditions with simple 1D ^{19}F NMR spectra.

Acknowledgment: project was supported by UMO-2021/41/B/ST4/03807 from the Polish Scientific Committee.



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sciforum-167799: Study on the cytotoxic and antioxidant activity of novel 1,3-disubstituted-benzimidazol-2-imine hydrazones

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Cancer encompasses a heterogeneous group of more than 100 diseases characterized by uncontrolled cell proliferation with the potential for invasion and metastasis, ultimately leading to severe organ dysfunction. Among men, the most frequently diagnosed cancers include lung, prostate, colorectal, and gastric cancer, whereas breast and cervical cancers predominate in women. One of the major challenges in effective cancer treatment is the ability of malignant cells to evade immune surveillance, as well as the distinct tumor microenvironment, which is often characterized by altered pH, elevated glutathione levels, and increased peroxide production.

Conventional cancer therapy relies predominantly on chemotherapy due to its pronounced cytotoxic effects. However, the lack of selectivity associated with chemotherapeutic agents frequently results in significant adverse effects, including myelosuppression, increased susceptibility to infections, fatigue, nausea, cognitive impairment, and muscle wasting. These limitations have driven growing interest in the development of more selective and targeted therapeutic strategies, particularly advanced drug-delivery systems. In this context, nanoparticle-based platforms and their functionalization have emerged as promising approaches to enhance therapeutic efficacy while minimizing systemic toxicity.

In the present study, a series of five novel derivatives of 1H-benzimidazol-2-amine were synthesized via a base-catalyzed nucleophilic addition reaction. The chemical structures and purity of the synthesized compounds were confirmed using ¹H NMR, ¹³C NMR, infrared spectroscopy, and mass spectrometry. Following structural validation, the compounds were evaluated for their antioxidant properties and cytotoxic activity against HeLa, HT29, and A549 cancer cell lines. The obtained results demonstrated satisfactory IC₅₀ values, highlighting the potential of these derivatives as promising candidates for further development as anticancer agents.

This research was funded by the Bulgarian national science fund, project № КПО6-Китай/6 16.12.2024.



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sciforum-178017: Synthesis of Morpholine Dithiocarbamate Indole

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Indoles are privileged heterocyclic scaffolds widely present in natural products and pharmaceutical agents. Among them, 3-dithiocarbamate indoles have emerged as valuable structural motifs due to their promising biological activities and pharmaceutical potential. Incorporation of a dithiocarbamate (DTC) moiety into the indole core provides a versatile platform for structural diversification and modulation of physicochemical properties. In particular, morpholine-derived DTC are attractive because the morpholine unit is a well-established pharmacophore with favorable metabolic and pharmacokinetic characteristics. Direct incorporation of DTC groups at the C3 position of indoles represents a straightforward and atom-economical strategy for constructing indole-DTC frameworks. However, despite its conceptual simplicity, only limited methods have been reported for the direct introduction of DTC moieties into heterocycles. Existing approaches generally rely on transition-metal catalysis, radical-mediated pathways, or oxidative systems, which may require harsh reaction conditions, metal reagents, or moisture-sensitive components. Herein, we report an efficient iodine-based oxidative protocol employing sodium iodide (NaI) and an oxidant in a DMSO/H₂O system to achieve C-S bond formation at the C3 position of indoles. The reaction proceeds under mild, operationally simple, and moisture-insensitive conditions, affording morpholine-containing 3- DTC indoles in good yields. This practical method provides streamlined access to pharmacologically relevant indole derivatives for further biological evaluation.



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Session 3. Natural Products in Drug Discovery

sciforum-178229: Discovery of Noscapienes derivatives as Novel and Potent Agents for the Treatment of Glioblastoma

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Glioblastoma (GBM) is the most aggressive and lethal primary brain tumor in adults, with extremely poor prognosis and high recurrence rate. The development of new, effective, and safe chemotherapeutic agents for the treatment of GBM remains an urgent and unmet clinical need in current drug discovery and oncology research. Herein, we designed and synthesized a series of novel noscapine derivatives by strategically replacing the N-methyl group of noscapine with an N-dimethylcarbamoyl group, combined with structural modifications at other key sites of the noscapine scaffold to optimize its anti-GBM activity. Among all the synthesized derivatives, 9'-bromo-N-dimethylcarbamoyl-noscapine (JX43301) showed significantly superior in vitro anti-GBM potency compared to the parent compound noscapine. Specifically, JX43301 exhibited potent inhibitory effects on GBM cell proliferation in vitro, with IC₅₀ values of 0.32 μ M against U87 cells and 1.22 μ M against U118 cells, which were much lower than those of noscapine. Further functional studies demonstrated that JX43301 could efficiently suppress the migration and invasion of GBM cells, as well as induce G2/M phase cell cycle arrest, thereby inhibiting GBM cell progression. In addition, in vivo antitumor experiments confirmed that JX43301 displayed excellent anti-GBM activity, achieving a tumor growth inhibition (TGI) rate of more than 80%, which indicated its potential clinical application value. Mechanistic investigations further revealed that JX43301 exerted its anti-GBM effects by targeting CAMK2D to disrupt cellular calcium homeostasis, providing a clear molecular mechanism for its antitumor activity. Collectively, the N-dimethylcarbamoyl modification strategy on noscapine provides a promising direction for the development of novel anti-GBM chemotherapeutic agents, and JX43301 serves as an attractive lead compound for further structural optimization and preclinical research.



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sciforum-167778: *In vitro* Biological Activities of Extracts from *Uncaria macrophylla* Wall., Rubiaceae

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Introduction

Uncaria macrophylla Wall. (Rubiaceae) was extensively used in folk medicine. In Vietnam, research into its biological activities remain limited, despite its inclusion in the “List of 100 medicinal plants with high medical and economic value prioritized for development during the 2020–2030 period” issued by the Ministry of Health. This species contains diverse phytochemical constituents and has shown promising potential for antibacterial and anti-inflammatory applications.

Objectives and methods

This study aimed to investigate *in vitro* antibacterial and anti-inflammatory activities of extracts from different parts of *Uncaria macrophylla*. Branches, leaves, and hooks were collected in Thanh Hoa Province, Vietnam. Plant identification was carried out based on morphological characteristics. Preliminary phytochemical screening was performed. Crude extracts were obtained by ultrasonic-assisted extraction and maceration using 50% ethanol, followed by liquid–liquid partitioning. Antibacterial activity was evaluated using the agar well diffusion method, and minimum inhibitory concentrations (MICs) were determined by the solid medium dilution method. Anti-inflammatory activity was assessed by the egg albumin denaturation inhibition assay.

Results and Discussion

Phytochemical screening revealed the presence of alkaloids, flavonoids, triterpenoids, and cardiac glycosides. The extracts exhibited antibacterial activity against three Gram-positive bacterial strains, including methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Bacillus cereus*, with MIC values ranging from 1.25 to 20.00 mg/mL. Leaf extracts showed the strongest antibacterial activity. In addition, the extracts demonstrated notable anti-inflammatory activity, with IC_{50} values ranging from 1.01 to 4.89 mg/mL, comparable to the positive control diclofenac sodium ($IC_{50} = 1.69$ mg/mL). Among the tested samples, hook extracts exhibited the most potent anti-inflammatory effects. Overall, extracts obtained by maceration exhibited higher biological activities than those obtained by ultrasonic-assisted extraction.

Conclusion

Uncaria macrophylla Wall. possesses significant *in vitro* antibacterial and anti-inflammatory activities. Extracts from leaves and hooks prepared by maceration showed the most promising results.



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sciforum-166932: *Paeonia lactiflora* as a valuable source of novel bioactive phytochemicals with promising potential for skin and oral care health

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Paeonia lactiflora has been widely used in traditional Asian medicine, primarily for pain relief and the treatment of inflammatory-related diseases. The roots of *P. lactiflora* are rich in monoterpene glycosides and phenolic molecules, among which paeoniflorin is considered the major bioactive compound, characterized by a favorable safety profile and diverse pharmacological activities.

This study aimed to evaluate the novel effects of *P. lactiflora* root extract standardized for paeoniflorin on inflammatory and barrier-related targets in the skin and oral mucosa.

In silico docking, molecular dynamics, and MM/PBSA simulations were performed to predict the interaction of paeoniflorin with transient receptor potential vanilloid 1 (TRPV1) and matrix metalloproteinases (MMPs). Additionally, protein–small molecule interaction network analysis was conducted using Cytoscape and the IntAct database. Inflammatory mediators and tissue destruction markers were quantified by ELISA. The maximum tolerated concentration in skin keratinocytes was determined to be 0.5 mg/mL using the MTT assay.

The extract significantly reduced TRPV1 expression in HaCaT keratinocytes and attenuated LPS-induced inflammation, decreasing TNF- α synthesis and reducing IL-6, IL-13 levels by up to 25% (P 0.01) and 55% (P 0.001), respectively. A significant protective effect against tissue degradation was observed through reducing MMP-9 production by 70.27% in dermal fibroblasts and MMP-8 production in gingival fibroblasts by 39.32% (P 0.001).

Furthermore, paeoniflorin reduced the release of volatile sulfur compounds such as H₂S and CH₃SH by up to 50% *in vitro*. These compounds are associated with halitosis, a common comorbidity of periodontal inflammatory disorders, indicating relevance for oral care applications. Long-term studies demonstrated that the extract remained stable in oral care formulations for 84 days under thermal stress conditions, corresponding to three years of product storage.

In conclusion, *P. lactiflora* root extract demonstrates strong potential for modulating inflammatory, sensory, and barrier-related pathways in the skin and oral mucosa cells.



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sciforum-167617: *Paeonia Veitchii*-Derived Bioactive Components as Dual-Action Intracanal Medications

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Objective

This study aimed to investigate the antibacterial and anti-inflammatory properties of bioactive compounds derived from *Paeonia veitchii* and assess their potential as dual-function intracanal medications on killing *Enterococcus faecalis* and inhibiting inflammation.

Methods

Three active components, paeoniflorin, chlorogenic acid, and proanthocyanidin, were evaluated individually and in combination for their effects against *E. faecalis* and inflammatory macrophages induced by LPS. Antibacterial and antibiofilm activities were assessed using microbial susceptibility testing, crystal violet biofilm staining, and SEM. Preliminary mechanisms were examined through membrane integrity observation, metabolic activity measurement, and qRT-PCR. Anti-inflammatory activity was determined via qRT-PCR and WB, and underlying pathways were predicted using network pharmacology and WB.

Results

Each component alone inhibited planktonic growth and biofilm formation of *E. faecalis* at moderately elevated concentrations. Pairwise combinations demonstrated enhanced efficacy, reducing effective concentrations by approximately half. The agents acted through membrane disruption, suppression of energy metabolism, and downregulation of virulence genes related to adhesion, biofilm formation, survival, tissue damage, and stress response. Furthermore, the compounds significantly reduced gene and protein expression of IL-6, IL-1 β and TNF- α in macrophages, and pairwise combinations were more effective. Network pharmacology analysis and WB indicated that these effects may involve modulation of the PI3K-Akt, NF- κ B and ERK signaling pathways.

Conclusions

The active constituents of *Paeonia veitchii* exhibit promising dual antibacterial and anti-inflammatory properties, supporting their potential as intracanal therapeutics. The synergistic effect observed in combination suggests a viable strategy to enhance the bioactivity of plant-derived compounds for clinical application.



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sciforum-178008: Angelic Acid Prevents RANKL-Induced Osteoclastogenesis Through Pathway-Biased Inhibition of MAPK–NFATc1 Signaling

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Excessive osteoclast activity drives inflammatory bone loss in diseases such as osteoporosis, rheumatoid arthritis, and periodontitis. Natural products represent an important source of bioactive molecules with therapeutic potential; however, relatively few compounds exhibit pathway-biased mechanisms of action during osteoclast differentiation. Here, we investigated the effects of angelic acid, a naturally occurring unsaturated monocarboxylic acid, on receptor activator of nuclear factor- κ B ligand (RANKL)-induced osteoclastogenesis.

Murine osteoclast precursor cells were stimulated with RANKL in the presence of angelic acid to evaluate its effects on osteoclast differentiation. Cell viability assays demonstrated that angelic acid showed no detectable cytotoxicity at concentrations used for osteoclastogenesis assays. TRAP staining revealed that angelic acid significantly reduced the formation of TRAP-positive multinucleated osteoclasts in a concentration-dependent manner, with an IC_{50} of approximately 1.9 μ M.

Mechanistic investigations demonstrated that angelic acid preferentially suppresses MAPK signaling, including ERK, p38, and JNK phosphorylation, while NF- κ B transcriptional activity remains largely unaffected, indicating pathway-biased inhibition. Consistent with impaired MAPK signaling, angelic acid blocked nuclear translocation of NFATc1 and significantly reduced expression of osteoclast-associated genes including TRAP, cathepsin K, and Atp6v0d2.

Collectively, these findings identify angelic acid as a potent inhibitor of osteoclast differentiation acting through MAPK-dependent regulation of NFATc1, providing a mechanistic basis for its potential therapeutic application in bone-resorptive diseases.



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sciforum-180450: Studies towards the Asymmetric Total syntheses of Emetine-type Alkaloids Deoxytubulosine with Antitumoral Bioactivity

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A family of monoterpenoid alkaloids, bearing structural resemblance to emetine, is widely distributed among various plant species, including *Carapichea ipecacuanha*, *Alangium longiflorum*, *Pogonopus tubulosus*, and *Ochrosia lifuana*. These alkaloids are characterized by a quinolizidine core linked to two Pictet–Spengler–derived units—typically tetrahydroisoquinoline (THIQ) or tetrahydro- β -carboline (THBC). Preliminary phytochemical studies have facilitated the isolation of a series of emetine-type alkaloids from *Alangium salviifolium*. Among them, biological assays revealed that deoxytubulosine exhibits favorable antitumor bioactivity at the micromolar level, and further flow cytometric analysis demonstrated that this compound can effectively induce cell cycle arrest. In this work, a chiral-pool synthesis strategy employing cost-effective D-aspartic acid derivatives as starting materials was developed for the asymmetric total synthesis of deoxytubulosine. The core piperidine ring bearing multiple stereogenic centers was constructed through a nickel-catalyzed ene-yne cyclization, which delivers exceptional stereochemical control to afford only a single stereoisomer. The double bond derived from this cyclization can be hydrogenated under different conditions to realize divergent stereoselective control. The tetrahydroisoquinoline moiety was efficiently assembled via a decarbonylative Pictet–Spengler reaction. This synthetic approach shows remarkable potential for diversity-oriented synthesis, and the key building block obtained may serve as a versatile precursor for the preparation of a wide range of structurally diverse monoterpenoid alkaloids.



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sciforum-177872: synthesis and anti-inflammatory activity of piperine derivatives from natural products

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Introduction

Inflammation is a crucial physiological defense mechanism; however, persistent inflammation is closely associated with various chronic diseases. Although non-steroidal anti-inflammatory drugs (NSAIDs) are widely used, their long-term administration may lead to adverse effects such as gastrointestinal ulcers. Thus, the development of novel therapeutics with improved efficacy and selectivity remains an urgent priority.

Methods

In this study, piperine was selected as the lead compound. Structural modifications were performed on its amide piperidine ring and aliphatic olefin chain based on molecular hybridization principles, introducing anti-inflammatory pharmacophores including phenyl-1,2,3-triazole fragments. Cytotoxicity of piperine derivatives (10 μ M) on murine macrophage RAW 264.7 cells was evaluated via MTT assay. Griess reagent and ELISA kits were employed to assess inhibitory effects on LPS-induced nitric oxide (NO) and interleukin-6 (IL-6) production. Molecular docking studies using Schrödinger platform were conducted to elucidate binding modes with TLR4 (PDB ID: 2Z62).

Results

Three series of 30 piperine derivatives were designed, synthesized, and characterized by ^1H NMR, ^{13}C NMR, and HRMS. MTT assays revealed that 19 derivatives exhibited no cytotoxicity (cell viability >85%). In NO inhibition assays, 17 compounds demonstrated stronger inhibitory activity compared to dexamethasone. Compound A6 exhibited the highest NO inhibition rate (87.7% at 10 μ M) and significantly inhibited LPS-induced IL-6 production (84.6% at 10 μ M). Molecular docking revealed that A6 bound to TLR4 with a docking energy of -6.815 kcal/mol, superior to piperine (-5.285 kcal/mol).

Conclusion

Derivative A6, featuring incorporation of a meta-iodophenyl-1,2,3-triazole moiety into the piperidine amide ring while retaining the aliphatic olefin chain, demonstrates promising in vitro anti-inflammatory activity, laying a foundation for novel therapeutic development.



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sciforum-177997: 8-Epixanthatin Suppresses RANKL-Induced Osteoclast Differentiation via Inhibition of NF- κ B and MAPK Signaling

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Osteoclast hyperactivity represents a central mechanism underlying pathological bone destruction in diseases such as osteoporosis, rheumatoid arthritis, and cancer-associated bone loss. Excessive osteoclast differentiation and activation lead to increased bone resorption, highlighting the importance of identifying novel small molecules that can inhibit osteoclastogenesis and serve as potential therapeutic agents.

In this study, we investigated the effects of 8-Epixanthatin, a natural sesquiterpene lactone, on RANKL-induced osteoclast differentiation. Murine osteoclast precursor cells were stimulated with receptor activator of nuclear factor- κ B ligand (RANKL) in the presence of 8-Epixanthatin. Cell viability assays demonstrated that the compound exhibited no significant cytotoxicity at the concentrations used for osteoclast differentiation studies. TRAP staining revealed that 8-Epixanthatin significantly reduced the formation of TRAP-positive multinucleated osteoclasts in a concentration-dependent manner, with an IC_{50} value of approximately 2.3 μ M.

Mechanistic investigations further demonstrated that 8-Epixanthatin interferes with RANKL-activated intracellular signaling pathways. Specifically, the compound suppressed activation of the NF- κ B and MAPK signaling cascades, which play essential roles in regulating osteoclast differentiation and function. Inhibition of these pathways suggests that 8-Epixanthatin disrupts key transcriptional programs required for osteoclastogenesis.

Collectively, these findings identify 8-Epixanthatin as a promising lead compound for the development of anti-osteoclast therapeutics and highlight its potential relevance in the treatment of pathological bone resorption disorders.



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sciforum-165999: Anti-osteoporosis lead compounds from marine fungi

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Osteoporosis is known as a common bone disease that poses a severe public health threat owing to the increased ageing population. Targeting osteoclast differentiation has been an effective therapeutic strategy for osteolytic diseases including osteoporosis. The clinically commonly used therapeutic agents carry serious complications and intolerable side effects. Therefore, novel osteoclast differentiation inhibitors with new modes of action are urgently needed.

Marine-derived natural products have been recently evidenced as important sources of anti-osteoporotic lead compounds. Over 150 marine-derived natural products have been found with anti-osteoporotic activity, predominantly polyketides and terpenoids sourced from marine fungi. As far as our continuing endeavors searching for naturally occurring potent osteoclast differentiation inhibitors from marine fungi, a network of structurally diversified compounds was recently characterized, including indole diterpenoids, azaphilones, tanzawaic acids, depsidones, and nitrobenzoyl sesquiterpenoids. Among them, brefeldindole E suppressed RANKL-induced osteoclast differentiation without observed cytotoxicity in BMMs, leading to the suppression of nuclear translocation of NFATc1 and downregulation of the expression of osteoclast-related fusion protein DC-STAMP. Notably, penicisteck acid F showed potent NF- κ B inhibitory activity and remarkably inhibited osteoclast generation *in vitro*. Mechanistically, it reduced RANKL-induced I κ B α degradation, NF- κ B p65 nuclear translocation, the activation and nuclear translocation of NFATc1, and the relevant mRNA expression. It further alleviated osteoporosis in ovariectomized mice by reducing the quantities of osteoclasts, suggesting a novel potential inhibitor of osteoclastogenesis and osteoporosis for further development of potent antiosteoporosis agents.



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sciforum-166935: Antibacterial potential of modified analogs of Aurein 1.2

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Introduction

Antimicrobial resistance (AMR) represents a significant global threat to public health and sustainable development. The failure of traditional antimicrobial therapies has resulted in a pressing need for new classes of antimicrobial agents, which have not been applied so far. The AMPs are promising to be effective alternatives to antibiotics, particularly against multidrug-resistant pathogens and thus be a possible solution to the escalating problem of antimicrobial resistance.

Methods

The modification of Aurein 1.2 and the investigation of its antibacterial behavior were the focus of this study. This family of antibacterial peptides are secreted from green and golden bell frog. The new analogues were obtained by the solid-phase peptide synthesis by substituting phenylalanine with a fluorinated one at the 3rd, 13th, and both positions and by substituting aspartate with lysin at the 4th position. The methods for determination of minimal inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were applied for evaluation of the antibacterial potential of new Aurein 1.2 analogs against Gram-negative strain *Pseudomonas aeruginosa* NBIMCC 3700 and Gram-positive strain *Staphylococcus aureus* NBIMCC 3703.

Results

Aurein 1.2 analogues, substituted with Lys residue in position 4 and two 4-fluorophenylalanine residues in positions 3 and 13 solely or in combination, also decreased MIC values against *S. aureus* 3703, compared to the original peptide (MIC = 160 µg/ml). The values of MBC against *S. aureus* 3703 were higher than the MIC of the newly synthesized compounds, ranging from 20 to 160 µg/ml.

Conclusions

Among all compounds studied, the one containing a Lys residue at position 4 and a 4-fluorophenylalanine residue at position 13 exhibited the strongest activity against both strains.

Acknowledgment

This study is funded by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0002, "BiOrgaMCT".



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sciforum-167456: Antioxidant and Tyrosinase-Modulating Properties of Collagen Extraction from *Euthynnus affinis* Bones

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Fish collagen has attracted considerable attention as a marine-based resource due to its biocompatibility, safety, and potential biological activities relevant to cosmetic applications. This study aimed to evaluate the potential of collagen extracted from the bones of *Euthynnus affinis* as an antioxidant and a tyrosinase-modulating agent for halal skin-brightening cosmetic application. Collagen was extracted using a wet extraction method, preceded by alkaline pretreatment with 0.1 M NaOH to remove non-collagenous proteins, followed by acid extraction with 0.5 M acetic acid assisted by microwave irradiation at 100 W. The obtained collagen was characterized using Fourier Transform Infra Red (FTIR) spectroscopy to assess functional groups and molecular structural integrity. Antioxidant activity was evaluated using the DPPH radical scavenging assay, while tyrosinase activity was assessed spectrophotometrically using L-DOPA as the enzymatic substrate. The results showed a collagen yield of $22.71\% \pm 6.24$, with FTIR spectra displaying characteristic collagen absorption bands (Amide A, I, II, dan III), indicating that the molecular structure of collagen was well preserved. The collagen exhibited moderate to strong antioxidant activity based on its DPPH IC_{50} value. Although direct tyrosinase inhibitory activity was relatively weak, the antioxidant properties suggest a potential indirect modulation of melanogenesis through the reduction of oxidative stress. In conclusion, collagen derived from *Euthynnus affinis* bones demonstrates promising antioxidant activity and favorable structural characteristics, supporting its potential use as a natural, halal, and sustainable supporting ingredient in skin-brightening cosmetic formulation



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sciforum-178009: Asarinin Suppresses RANKL-Induced Osteoclast Differentiation by Targeting the p38/ERK–c-Fos–NFATc1 Axis

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Excessive osteoclast differentiation and activation contribute to pathological bone loss associated with diseases such as osteoporosis, rheumatoid arthritis, and metastatic bone disease. Identification of small molecules capable of modulating osteoclastogenesis is therefore important for the development of new anti-resorptive therapies. Natural products represent a valuable source of pharmacologically active compounds with diverse biological activities.

In this study, we investigated the effects of asarinin, a naturally occurring lignan compound, on receptor activator of nuclear factor- κ B ligand (RANKL)-induced osteoclast differentiation. Murine osteoclast precursor cells were stimulated with RANKL in the presence of asarinin to evaluate its impact on osteoclast formation. Cell viability assays indicated that asarinin exhibited no significant cytotoxicity at concentrations used in osteoclastogenesis assays. TRAP staining demonstrated that asarinin markedly reduced the formation of TRAP-positive multinucleated osteoclasts in a concentration-dependent manner.

Mechanistic analyses revealed that asarinin interferes with key signaling pathways involved in osteoclast differentiation. Specifically, asarinin suppressed phosphorylation of MAPK components p38 and ERK following RANKL stimulation. Inhibition of these pathways resulted in reduced expression of the transcription factor c-Fos and subsequent downregulation of NFATc1, the master regulator of osteoclastogenesis. Consistent with these effects, expression of osteoclast-associated genes was significantly decreased.

Collectively, these findings demonstrate that asarinin inhibits osteoclast differentiation by targeting the p38/ERK–c-Fos–NFATc1 signaling axis and highlight its potential as a promising natural compound for therapeutic development against pathological bone resorption.



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sciforum-177907: Chemical modification of natural alkaloids with heterocyclic reagents in the synthesis of compounds with a broad spectrum of biological action

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Introduction

Alkaloids are between the first plant compounds that attracted the attention of pharmacologists. Many natural and synthetic alkaloids have been widely used in clinical practice and have no worthy alternative. Chemical modification of this type of compounds has been firmly established as a promising route to the rational design of novel broad-spectrum drugs. An attractive strategy for such modification is the covalent fusion with the other pharmacophoric units with complementary activity and multiple pharmacological targets. The ability to interact with different targets, i.e. different mechanisms of action, of the separate parts of a hybrid drug can increase its effectiveness and reduce undesirable side effects. N-heterocycles are widely represented in the structure of bioactive natural compounds and drugs. Their inclusion can increase efficacy and improve pharmacokinetics of resulting conjugates.

Methods

Natural alkaloids were introduced into the reactions with N-heterocyclic acid chlorides, urethanes and azides. All products were selectively tested for antiviral, antifungal, antimicrobial, analgesic, antitumor activity and cytotoxicity. Molecular docking and quantum chemical calculations were used to explain possible causes of some biological effects observed.

Results

The approach used allowed to obtain anabasine, cytosine and quinine conjugates with isothiazole, isoxazole and pyridine joined by ester, urea and triazole linkers. Some quinine derivatives revealed very good antimicrobial activity (MIC = 7–8 μ M against *Staphylococcus aureus*), while quaternized anabasine esters have shown even more impressive results (MIC = 1.3 μ M against *Staphylococcus aureus*). It has been established that modification of quinine at the hydroxyl group increases its cytotoxicity. A pronounced synergistic effect of isoxazole-containing ureas based on anabasine and cytosine in combination with ribomustine and cisplatin was discovered.

Conclusions

Conjugation of natural alkaloids with N-heterocycles has shown itself to be a promising approach to obtaining pharmacologically useful compounds. Activity of selected derivatives allows considering them for further deeper properties study.



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sciforum-181473: Discovery and Total Synthesis of Anhydrotuberosin as a STING Antagonist for Treating Autoimmune Diseases

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Excessive activation of the stimulator of interferon genes (STING) pathway is a key pathological driver of numerous autoimmune and autoinflammatory diseases, such as STING-associated vasculopathy with infantile-onset (SAVI) and inflammatory bowel disease (IBD). To date, the development of potent, druggable STING antagonists remains challenging, creating an urgent unmet clinical need for targeted therapeutic agents. Here, we identified the natural product anhydrotuberosin (ATS) as a novel STING antagonist through high-throughput chemical screening and systematic biological validation. However, the extremely low abundance of ATS in natural sources severely restricts in-depth mechanistic research and preclinical pharmacological evaluation. To address this limitation, we established a concise, scalable six-step total synthetic route to achieve sufficient and stable preparation of ATS. Using synthetic compounds, we comprehensively clarified the molecular mechanism by which ATS suppresses abnormal STING signaling. Functional verification confirmed that ATS effectively inhibited hyperactivated STING activity in peripheral blood mononuclear cells from three SAVI patients. Furthermore, ATS exhibited favorable pharmacokinetic properties, significantly alleviated tissue inflammation in DSS-induced colitis and Trex1 knockout autoimmune animal models, and maintained excellent biosafety with low toxicity. Collectively, this study validates ATS as a promising lead compound, provides reliable synthetic technical support, and lays a solid preclinical foundation for developing novel STING-targeted drugs to treat refractory autoimmune and autoinflammatory disorders.



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sciforum-165849: Dunaliella salina-loaded diosmetin carriers alleviate oxidative stress and inflammation in cisplatin induced acute kidney injury via PI3K/AKT pathway

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Background

As a widely used chemotherapeutic agent, cisplatin frequently induces acute kidney injury (AKI), which severely compromises patient survival and limits its clinical use. While the natural flavonoid diosmetin (Dio) shows promise in mitigating cisplatin induced nephrotoxicity, its clinical translation is challenged by poor solubility, low bioavailability, and incompletely elucidated mechanisms. This study aimed to overcome these limitations by developing a novel drug delivery system using the microalgae *Dunaliella salina* (D. salina, Ds) to load Dio (Ds-Dio), thereby enhancing its efficacy and exploring its therapeutic potential.

Methods

We first characterized the physicochemical properties of Ds and Dio, and then Ds-Dio complex was synthesized via co-incubation. Its nephroprotective efficacy and safety were systematically evaluated in a cisplatin-induced mouse AKI model by assessing renal function (serum creatinine, blood urea nitrogen), injury biomarkers, histopathology, body weight and organ index. The underlying mechanism was predicted by network pharmacology and subsequently validated experimentally.

Results

The novel Ds-Dio delivery system has been successfully established. In the AKI model, Ds-Dio significantly improved renal function and exhibited a superior protective effect over Dio alone, a benefit attributed to the enhanced bioavailability provided by Ds carrier. Besides, Ds-Dio also demonstrated the safety performance, with no evidence of toxicity to major organs. Network pharmacology analysis predicted the involvement of PI3K/AKT pathway, which was experimentally verified. Specifically, we confirmed that Ds-Dio alleviates AKI by modulating the PI3K/AKT pathway, resulting in concurrent suppression of NF- κ B mediated inflammation and activation of NRF2 dependent antioxidant responses.

Conclusion

This study successfully developed a microalgae-based drug delivery system, Ds-Dio, which significantly enhances the nephroprotective efficacy of Dio against cisplatin-induced AKI. The nephroprotective mechanism is mediated through the PI3K/AKT pathway, resulting in the simultaneous attenuation of oxidative stress and inflammation.



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sciforum-167769: Effect of *Andrographis paniculata* extract and andrographolide on CYP2C9 expression in the livers of diabetic rats treated with glipizide

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Andrographis paniculata extract (APE) and its major compound, andrographolide (AND), have great potential as antidiabetic therapeutic agents. However, administering APE and AND in patients with diabetes can affect the activity of enzymes that metabolize oral antidiabetic drugs, potentially leading to herb-drug interactions. This study aims to prove pharmacokinetic interactions by measuring CYP2C9 mRNA expression in diabetic rats treated with glipizide. Streptozotocin- and nicotinamide-induced diabetic rats were given a single treatment of glipizide (GLZ) and a combination of APE and AND for 21 days. mRNA from the rat liver was isolated, and its expression was measured using qRT-PCR. The $2^{\Delta\Delta CT}$ value was calculated and used to predict the relative mRNA expression in each treatment group. One-way ANOVA with a 95% confidence interval was performed in GraphPad Prism. The results showed that, compared with GLZ alone, co-administration with APE did not significantly affect CYP2C9 mRNA expression, the main enzyme involved in GLZ metabolism. Meanwhile, AND administration increased (p value 0.05) CYP2C9 mRNA expression, suggesting it may affect GLZ metabolism and impact blood drug levels and pharmacological effects. This study can serve as a basis for predicting potential HDI and is an important test to be carried out in the development of new drugs that could be used as complementary therapies for diabetes mellitus.



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sciforum-177850: Effects of new compound DCE-1 on cognitive impairment in an Alzheimer's disease models

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Background

Alzheimer's disease (AD) is a multi-factorial dementia for which effective multi-target therapeutic agents are currently unavailable. Research has found catechins can effectively improve cognitive dysfunction. This study aims to evaluate the effect of a new catechin derivative DCE-1 on cognitive impairments in a scopolamine-induced AD-like mouse model using behavioral tests, and to explore the biological functions regulated.

Methods

Evaluation of cognitive performance after DCE-1 administration using scopolamine induced mouse dementia model via the Elevated Plus Maze (EPM) and Y-maze tests. The OGD/R model in SH-SY5Y cells, the LPS model in BV-2 cells, and the phagocytosis model in BV-2 cells were employed to explore the effect of DCE-1 on oxidative stress, inflammation, and phagocytosis.

Results

The DCE-1-treated groups demonstrated memory retention in the EPM and Y-maze tests similar to that of the Donepezil group. In vitro, DCE-1 decreased cell death and the levels of intracellular ROS and Ca^{2+} in SH-SY5Y under OGD/R, and reduced the release of NO induced by LPS in BV-2. Moreover, DCE-1 promoted BV-2 cell phagocytosis of $\text{A}\beta_{1-42}$.

Conclusion

These results showed that DCE-1 alleviates AD-like pathology by suppressing oxidative stress, neuroinflammation and facilitate phagocytosis. Thus, DCE-1 is considered to have the potential to improves the phenotypic characteristics of Alzheimer's disease by regulating multiple biological functions.



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sciforum-167709: Exploring the Collagen Potential from Fish in the Waters Around Cilacap, Indonesia: Extraction and Physicochemical Characterization

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Collagen is a critical structural biomolecule extensively utilized in pharmaceuticals, particularly as a biomaterial for drug delivery systems, biomedical scaffolds, and protein-based formulations. The predominant commercial sources of collagen are cows and pigs, highlighting the necessity for alternative sources that are safer, more sustainable, and compliant with halal standards. Fish represent a promising alternative due to their diverse structural properties. This study evaluates 15 fish species from Cilacap waters, Indonesia, as potential collagen sources, with a focus on yield and molecular structure quality to identify candidates for pharmaceutical and medicinal chemistry applications. Collagen was extracted from skin and bone using acetic acid hydrolysis. The molecular structure was analyzed by Fourier Transform Infrared (FTIR) spectroscopy, with emphasis on the amide bands. Principal Component Analysis (PCA) of the spectral data revealed interspecies differences in structural characteristics. The results demonstrate that collagen from Indian anchovy (*Stolephorus indicus*) exhibits superior molecular structural integrity, as indicated by the Amide III/1450 intensity ratio and a complete amide band profile, suggesting preservation of the triple helix structure. Although the yield is moderate, the high molecular quality positions this species as a strong candidate for further development in drug delivery systems and protein-based biomaterials. In contrast, species such as bigeye scad (*Selar crumenophthalmus*), black pomfret (*Parastromateus niger*), and Indian mackerel (*Rastrelliger kanagurta*) provide higher collagen yields while maintaining adequate structural characteristics, indicating their potential suitability for pharmaceutical applications with optimized extraction processes.



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sciforum-165127: Identification of Chalcone 17 and Chalcone 30 Protein Targets in the nematode *Caenorhabditis elegans*: new nematocides mode of action (MOA)

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Plant-parasitic nematodes (PPNs) threaten global food production, with *Meloidogyne incognita* (root-knot nematodes, RKNs) being a major concern due to their ability to damage plant roots, reducing crop yields. Current control methods, including synthetic chemical fumigants, are harmful to humans and the environment. Chalcones, plant-derived precursors to flavonoids, have shown promising nematocidal effects, but their mechanism of action remains unknown. Our working hypothesis is that chalcones inhibit a nematode protein by binding to its active site, preventing its function; mutations in the corresponding gene may alter protein conformation, preventing chalcone binding and leading to resistance. To investigate this, our lab used *Caenorhabditis elegans* as a model organism. Previously, whole-genome sequencing followed by bioinformatics approach on ethyl methanesulfonate (EMS) generated resistant mutant lines, identified candidate genes linked to resistance. The current study aimed to validate candidate genes responsible for *C. elegans* resistance to Chalcone 17 (the candidate genes are *sly-1*, Y62H9A.8, Y53F4B.21, C30D11.5, C50E10.13) and 30 (the candidate genes are *clcc-9*, *cyp-13A10*, *gst-5*, *ifb-2*, K06A9.1) using CRISPR-Cas9. Single guide RNAs (sgRNAs) were designed, editing efficiency of each guide was tested *in vitro*, and visualized via agarose gel electrophoresis to detect shifts in gene sequence size after digestion. Microinjection facilitated *in vivo* delivery of sgRNAs for gene editing. Our findings identified *ifb-2*, an intermediate filament (IF) protein gene expressed in the intestine, as responsible for Chalcone 30 resistance. For Chalcone 17 resistance, we identified *sly-1*, a gene encoding a Sec1 family domain protein involved in vesicle transport from the endoplasmic reticulum to the Golgi. Our findings are significant in that they identify new ways in which nematocides can control nematodes specifically.



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sciforum-159911: Integrated Phytochemical, Biological, and Chemometric Analysis of the Apoptosis-Inducing Ethyl Acetate Extract from *Varthemia sericea* Leaves

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Introduction

The ethyl acetate (EtOAc) extract of *Varthemia sericea* leaves was identified as the most promising fraction for cytotoxicity. This study provides a comprehensive phytochemical, biological, and computational characterization, employing multivariate statistics to decipher its bioactive profile.

Methods

Cytotoxicity was determined by MTT assay against MCF-7, HeLa, and HL60 cells (4–96 h). Phytochemical profiling was performed via UPLC-ESI-MS/MS. Apoptosis was investigated via fluorescent microscopy (Annexin V-FITC/PI) and a Caspase Multiplexing Assay. Selectivity was assessed on normal skin cells (LIVE/DEAD™ assay, 7h). *In silico* studies included molecular docking of major compounds against key targets (e.g., Bcl-2, ER α , Caspase-3; from PDB) and ADMET prediction (SwissADME/admetSAR). Multivariate statistical analysis (PCA, HCA) was applied to the LC-MS dataset to model chemical variance.

Results

The EtOAc extract demonstrated significant, time-dependent cytotoxicity (IC₅₀ 16.15 to 45.22 μ g/mL at 72 h). UPLC-ESI-MS/MS identified p-coumaric acid (72.77%) as dominant. PCA and HCA of the phytochemical data clearly segregated the EtOAc extract based on its distinct phenolic acid-rich profile, with p-coumaric acid identified as the primary contributor to the variance (high loading score). Fluorescent microscopy confirmed a time-dependent increase in apoptotic cells, corroborated by caspase activation, alongside low toxicity to normal cells. Docking simulations supported strong binding affinities of the major compounds to pro-apoptotic targets. ADMET predictions indicated favorable drug-likeness.

Conclusions

The ethyl acetate extract of *V. sericea* is a potent and selective inducer of apoptosis. The integrated approach—combining chemometric analysis, *in vitro* assays, and *in silico* validation—strongly implicates its unique phenolic acid composition, led by p-coumaric acid, as the foundation of its bioactivity, recommending it for further development as an anticancer lead.



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sciforum-166470: Integrating Experimental Assays and Molecular Descriptors into a QSAR Model of Polyphenolic Antioxidant Activity

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Polyphenolic compounds constitute a diverse class of secondary plant metabolites that are widely recognized for their antioxidant and antiradical properties. Owing to their structural complexity and pronounced dependence of activity on subtle electronic and substituent effects, reliable prediction of their behavior remains challenging. Although numerous experimental and computational studies have addressed this problem, many existing approaches rely on small, static datasets and lack general applicability across structurally diverse compound classes.

In this work, we present the experimental foundation of an integrated framework aimed at linking antioxidant and antiradical activity measurements with molecular-level descriptors for subsequent QSAR modeling. A carefully selected set of polyphenolic compounds, including phenolic acids, flavonoids, and anthocyanidins, is investigated using three widely accepted *in vitro* assays: FRAP, ABTS, and DPPH. The compounds were chosen to ensure systematic variation in substituent number, type, and position, enabling meaningful analysis of structure–activity relationships while maintaining chemical diversity.

All experimental measurements were performed under uniform laboratory conditions and expressed in a consistent manner to facilitate direct comparison across assays. The resulting dataset serves as a reliable basis for integration with a wide range of molecular descriptors. By combining these data into predictive QSAR models, it becomes possible to determine the activities of polyphenolic compounds within the applicability domain purely *in silico*. This approach bypasses the need for additional laboratory testing, requiring only the SMILES codes of the molecules.

***Acknowledgments:** *This research was funded in whole or in part by the National Science Centre, Poland, grant number 2022/45/N/NZ7/O2264.*



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sciforum-167108: Isolation and Characterization of the Chemical Constituents of *Protea madiensis* (Oliv.) Leaves and Its Tyrosinase Inhibitory Activity

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Protea madiensis, is a medicinal plant found in Western and Eastern Africa, as well as Australia. The roots of *P. madiensis* is reported for its use as skin depigmentating agent in Rwanda and also used for wound healing. In this study, the leaves of *P. madiensis* were investigated for its chemical constituents, column chromatographic fractionation using different solvent systems, further purification using HPLC, isolation of bioactive compounds and their characterization. The leaves of *P. madiensis* were air-dried, extracted with 80 % methanol followed by drying with a rotatory evaporator. Successive chromatographic techniques gave six (6) known compounds whose structures were characterised accordingly as *beta*-sitosterol (1), catechin (2), *epi*-catechin (3), kamferol (4), quercetin glycoside (5) and quercetin rhamnoside (6). The structural elucidation of the isolated compounds was determined based on 1D and 2D NMR, and LC-MS spectroscopy, as well as compared with the available literature data. The tyrosinase inhibitory activities of the methanolic crude extract and isolated compounds were also determined *in vitro*. According to the results obtained, methanolic crude extract, compounds 3, 5 and 6 exhibited potent tyrosinase inhibitory activity against L-tyrosine substrates with percentage inhibition of 43.03, 68.20 and 65.20 (500 µg/mL) compared to the control (kojic acid, 99.80), respectively. This study is the first report on the phytochemical investigation of compounds 1–6 from a natural source, and the first report of the biological evaluation of the compounds against the tyrosinase enzyme. The results suggest that these compounds might become natural candidates to inhibit tyrosinase in the cosmetic industry which supports its use in skin depigmentation.



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sciforum-167775: Isolation of pure compounds from the chloroform fraction of the fruit of *Cullen corylifolium* (L.) Medik., Fabaceae

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Introduction

Cullen corylifolium (L.) Medik. (Fabaceae) is a medicinal plant with various biological activities, including antibacterial, anti-inflammatory, and antioxidant properties, and holds strong potential for applications in cosmeceuticals. The plant possesses a diverse chemical composition, among which bakuchiol, a meroterpenoid compound, is often referred to as a “plant-based retinol” and has attracted significant attention for its biological effects such as anti-inflammatory, antibacterial, antioxidant, acne-treating, anti-aging effects and skin-brightening properties.

Objectives and methods

The subject of this study was the fruit of *Cullen corylifolium* (L.) Medik., Fabaceae.

The fruits were extracted by ultrasonic-assisted extraction using methanol to obtain the crude extract. The crude extract was fractionated by liquid-liquid partition. The chloroform fraction was selected for compound isolation using classical column chromatography. The collected fractions were further purified by physical, chemical, or chromatographic methods to obtain pure compounds. Purity was evaluated by TLC and HPLC-PDA. Compound structures were elucidated by IR, MS, and NMR spectroscopy.

Results and Discussion

From 200 g of *Cullen corylifolium* fruits, ultrasonic methanol extraction yielded 50.05 g of crude extract (25% yield). Liquid - liquid partitioning resulted in 30 g of chloroform fraction (57% yield). From chloroform extract, column chromatography was performed to isolate four compounds. The chemical structures of these isolated compounds were elucidated based on spectroscopic methods. They were identified as (2S)-6-(2-hydroxy-3-methylbut-3-en-1-yl)-2-(4-hydroxyphenyl)-7-methoxychroman-4-one (18.9 mg), psoralen (250 mg), isopsoralen (621 mg), and bakuchiol (1.32 g). The purity of those compounds determined by HPLC-PDA was 99.43%, 99.11%, 97.61% and 95.39%, respectively.

Conclusion

Four compounds were isolated from *Cullen corylifolium*: (2S)-6-(2-hydroxy-3-methylbut-3-en-1-yl)-2-(4-hydroxyphenyl)-7-methoxychroman-4-one, psoralen, isopsoralen and bakuchiol. Bakuchiol exhibits significant potential for development in skincare products and may serve as a marker compound in the quality control of extracts derived from this medicinal plant.



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sciforum-169720: Natural product AW126 inhibits pancreatic cancer growth via TGF- β /MAPK pathway

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Introduction

Pancreatic cancer, with a dismal 5-year survival rate of only 9%, urgently requires novel therapeutic agents. Natural products offer a promising source for drug discovery due to their structural diversity and biocompatibility. This study investigates the anti-tumor mechanism of AW126, a novel compound derived from the *Ferula sinkiangensis* aiming to develop a new targeted strategy.

Methods

In vitro anti-proliferative and anti-migratory activities of AW126 were evaluated in four pancreatic cancer cell lines. Mechanistic studies included flow cytometry and cytokine analysis. The direct target was identified via proteomic profiling using an AW126-based PROTAC and validated by SPR, CETSA, computational modeling, and molecular biology techniques. *In vivo* efficacy and pharmacokinetics were assessed using a patient-derived xenograft (PDX) model and SD rats.

Results

We identified the natural product AW126 as a novel, direct inhibitor of TGF β 2. It demonstrated potent anti-proliferative and anti-migratory effects across multiple pancreatic cancer cell lines. Mechanistically, AW126 induced cell cycle arrest and apoptosis, while proteomic and subsequent validation studies confirmed its high-affinity binding to TGF β 2. This interaction led to the effective blockade of the downstream oncogenic MAPK signaling pathway. Furthermore, AW126 exhibited significant tumor growth inhibition in a PDX model, supported by a favorable preliminary pharmacokinetic profile, highlighting its promising *in vivo* efficacy and drug-like properties.

Conclusion

This study delineates AW126 as a novel, multi-targeting natural product that exerts its potent anti-pancreatic cancer activity primarily through direct TGF β 2 inhibition and subsequent blockade of the oncogenic MAPK cascade. Its concurrent modulation of related network components underscores a sophisticated mechanism. AW126 represents a compelling lead compound for the development of novel TGF β 2-targeted therapies.



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sciforum-159081: Neuroprotective effects of Δ^9 -THC in the SOD1G93A mouse model of amyotrophic lateral sclerosis: modulation of protein aggregation and glia-driven neuroinflammation

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Introduction

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC) has emerged as a potential neuroprotective agent in amyotrophic lateral sclerosis (ALS). However, its impact on key pathogenic mechanisms such as protein aggregation and glia-mediated neuroinflammation remains insufficiently characterized. We investigated the therapeutic effects of Δ^9 -THC in the SOD1G93A mouse model of ALS, with emphasis on neuronal preservation, inflammatory responses, and muscle pathology.

Methods

Transgenic SOD1G93A mice received chronic treatment with a botanical drug substance of Δ^9 -THC (Δ^9 -THC-BDS; Jazz Pharmaceuticals Research UK Ltd), cannabidiol (CBD-BDS; Jazz Pharmaceuticals Research UK Ltd), or Δ^9 -THC-BDS combined with the mitochondrial modulator olexosime. Motor performance was longitudinally evaluated. Spinal cord pathology was assessed by quantification of Nissl- and ChAT-positive motor neurons, protein aggregation, glial reactivity, and inflammatory markers. Expression of muscle deterioration-related genes was also analyzed.

Results

SOD1G93A mice developed progressive motor deficits associated with motor neuron loss, increased astroglial and microglial activation, elevated inflammatory markers, accumulation of protein aggregates, and dysregulated muscle gene expression. Δ^9 -THC-BDS markedly attenuated disease progression, preserving motor neurons, reducing protein aggregation (consistent with enhanced autophagic clearance), normalizing inflammatory markers, and restoring muscle gene expression toward wild-type levels. CBD-BDS showed minimal efficacy. Combination therapy with Δ^9 -THC-BDS and olexosime produced certain potentiation for selected parameters.

Conclusions

Δ^9 -THC-BDS confers robust neuroprotection in SOD1G93A mice by reducing protein aggregation and attenuating glia-driven neuroinflammation. These effects are consistent with the activation of endocannabinoid-related signaling pathways, including cannabinoid receptors known to be involved in ALS pathophysiology, supporting the therapeutic potential of cannabinoid-based strategies.



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sciforum-167676: Optimizing the Bioactivity of Psychorubrin Through Chemical Derivatization: Studies in the Structure-to-Activity Relationship

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Psychorubrin is a small molecule natural product belonging to a class of compounds called pyranonaphthoquinones found in several plant species of the *Pentas* family, including the *lanceolata*, commonly called Egyptian star clusters, and the *longiflora* species, in the eastern Africa. Psychorubrin has become an appreciated active compound in several research areas of medicinal chemistry for its reported activity against a number of diseases such as malaria and various types of cancers. However, although this compound has proven to be a promising drug candidate, it also has high toxicity towards human cells rendering it unusable in medicinal applications. The current study delved into understanding the structural features of psychorubrin that are responsible for its high activity and/or high cytotoxicity via a chemical derivatization approach. The study aimed at identifying moieties within the psychorubrin molecule that can be chemically modified to reduce its cytotoxicity without losing its activity. Our preliminary results indicate that the naphthoquinone scaffold contributes significantly, although not solely, to the activity of psychorubrin, while the 3,4-dihydro-2H-pyran-2-ol moiety is more associated with the high cytotoxicity. Thus, chemical derivatization of the 3,4-dihydro-2H-pyran-2-ol moiety of psychorubrin that allows the attenuation of its bioactivity may alleviate its high cytotoxicity. This approach could deliver promising psychorubrin-derived drug candidates.



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sciforum-167631: Phosphodiesterase type 4 inhibitory activity of new FELL analogs

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Introduction

Phosphodiesterase type 4 (PDE4) inhibitors are known to serve as potent therapeutic agents for various inflammatory disorders such as asthma, chronic obstructive pulmonary disease, and psoriasis. However, conventional first-generation PDE4 inhibitors exhibit numerous side effects, making the pursuit of novel, safer alternatives essential. Bioactive peptides have recently gained much attention due to their small size, natural elimination mechanisms and minimal adverse effects [1]. FELL, a tetrapeptide originating from the human calcium-binding protein spermatid 1, shows significant anti-inflammatory properties [2]. The aim of the present work was to assess the PDE4 inhibitory activity of 5 new FELL analogs, substituted with D-Phe at position 1 and various hydrophobic amino acids (Leu, Nle, Ile and Val) at positions 3 and 4.

Methods

The FELL analogs were synthesized by a solid-phase peptide synthesis using the Fmoc/OtBu strategy [2]. Their PDE4 inhibitory activity was determined by using a microplate-based colorimetric assay [1].

Results

Five new structural FELL analogs were successfully synthesized. Their PDE4 inhibitory activity will be further discussed.

Conclusions

Introduction of D-Phe at position 1 significantly improved the PDE4 inhibitory activity of newly synthesized analogs. Among the tested FELL analogs, H-D-Phe-Glu-Nle-Nle-NH₂ showed the most potent PDE4 inhibitory activity.

Acknowledgements

This study is funded by the European Union-NextGenerationEU through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0002, “BiOrgaMCT” and by University of Reims Champagne-Ardenne.

References

1. Allart-Simon, I., Moniot, A., Bisi, N., Ponce-Vargas, M., Audonnet, S. Laronze-Cochard, M., Sapi, J., Henon, E., Velard, F., Gerard, S. RSC Med. Chem., 2021, 12, 584-592.
2. Borisova, B., Nocheva, H., Gérard, S., Laronze-Cochard, M., Dobrev, S., Angelova, S., Petrin, S., Danalev, D., Pharmaceuticals, 2023, 16, 1183.



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sciforum-173490: Phytocosmetic Creams: Composition, Technology, and Functional Properties

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The growing interest in plant-derived biologically active compounds has stimulated the development of phytocosmetic formulations with functional properties. This study aimed to develop and substantiate the composition and manufacturing technology of O/W emulsion creams containing extracts and essential oils obtained from plants of the flora of Kazakhstan. The formulations incorporated water–glycerin and ethanolic extracts rich in phenolic compounds, as well as vegetable oils, emollients, nonionic emulsifiers, humectants, antioxidants, and preservatives. The creams were produced using separate heating of the oil and aqueous phases followed by emulsification and incorporation of thermolabile phytocomponents at the cooling stage (35–40 °C).

The developed products were evaluated for organoleptic properties, pH, colloidal and thermal stability, rheological characteristics, microbiological purity, total phenolic content, and antioxidant activity by spectrophotometric methods. The results demonstrated that the inclusion of phytocomponents at concentrations of 1–5% did not adversely affect emulsion stability when nonionic emulsifiers were applied. The creams exhibited homogeneous consistency, pleasant sensory characteristics, and pH values within the physiological range of 5.2–5.8. Satisfactory colloidal stability and reproducible rheological behavior were observed. The presence of phenolic compounds contributed to measurable antioxidant activity.

The combination of water–glycerin and ethanolic extracts facilitated effective incorporation of both hydrophilic and lipophilic bioactive substances into the cream matrix. The findings support the feasibility of developing stable phytocosmetic creams enriched with plant-derived functional ingredients and confirm their potential for application in cosmetic products with antioxidant properties.



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sciforum-165572: Plant-Derived Substances as Promising Inhibitors of *Streptococcus mutans* Biofilm Formation

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Dental caries remains one of the most prevalent oral diseases worldwide, primarily associated with the ability of *Streptococcus mutans* to form stable biofilms on tooth surfaces. Biofilm-associated bacteria exhibit increased resistance to conventional antimicrobials, stimulating the search for alternative, naturally derived antibiofilm agents. Plant secondary metabolites represent a promising source of bioactive compounds with multitarget mechanisms of action and lower risk of resistance development. In the present study, selected medicinal plants were investigated as sources of antibiofilm agents against *S. mutans*. Plant materials were subjected to ultrasound-assisted extraction, and their chemical composition was identified using HPLC–UV–MS/MS. Essential oils were obtained by hydrodistillation using a laboratory-scale Clevenger apparatus, and their chemical profiles were analyzed by GC–MS. In addition, individual compounds were isolated from both essential oils and ethanolic plant extracts. The structures of the isolated compounds were elucidated using spectroscopic methods. Antibiofilm activity was assessed after 24 h using a crystal violet assay with spectrophotometric quantification of biofilm biomass relative to an untreated control. A number of plant extracts demonstrated a pronounced inhibitory effect on *S. mutans* biofilm formation, with inhibition levels reaching 90–100% compared to the control. As a result of the present study, it was demonstrated for the first time that the essential oils of *Origanum vulgare*, *Nepeta cataria* and *Salvia stepposa* exhibited the strongest suppressive activity against *S. mutans* biofilm formation in a medium containing 1% sucrose. The remaining essential oils showed inhibitory effects on *S. mutans* biofilm development in a concentration-dependent manner. The results confirm that selected plant-derived substances possess strong antibiofilm activity against *S. mutans* and may serve as promising candidates for the development of novel preventive dental formulations. These findings support further studies focused on mechanism elucidation, formulation development, and *in vivo* validation of plant-based antibiofilm agents for oral healthcare applications.



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sciforum-175266: Secondary Metabolites from Endophytic Fungus *Chromolaenica* sp. of Philippine Endemic Annonaceae Plant *Orophea cumingiana*

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The increasing prevalence of drug-resistant pathogenic bacteria has intensified the call for innovative strategies aimed at the discovery and development of novel antimicrobial agents. One effective way to enhance the production of bioactive secondary metabolites of fungi and induce antimicrobial compound biosynthesis is the One Strain–Many Compounds (OSMAC) approach. This method requires systematic modulation of cultivation parameters thereby expanding the chemical diversity and yield of secondary metabolites. In our continuing effort to search for novel antimicrobial compounds isolated from plant-derived fungus, we herewith attempted to isolate and purify secondary metabolites. As part of our ongoing search for novel antimicrobial compounds, we fermented 73 fungal endophytes isolated from different Philippine endemic plants on four different media: three liquid media [Yeast-Malt (YM), Zucker-Malt (ZM), and Baumwollsaatmehl (Q6)] and one solid brown rice containing BRFT (yeast extract) media. Among the fungal isolates, *Chromolaenica* sp. (accession number USTCMS 007.25) stood out. The methanolic extract obtained from BRFT culture exhibited significant antibacterial activity against five ESKAPE (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*) pathogens, with minimum inhibitory concentration (MIC) values ranging from 7.81 to 250 µg/mL and produced greater percent yield relative to other fungal extracts suggesting diverse myco-chemical constituents. The crude extract of *Chromolaenica* sp. isolated from the Philippine endemic Annonaceae species *Orophea cumingiana* (S. Vidal), was then subjected to systematic purification and isolation procedures. The structures of the isolated compounds were elucidated using spectroscopic analyses, including one- and two-dimensional nuclear magnetic resonance (1D and 2D NMR) spectroscopy, high-resolution mass spectrometry (HRMS) and infrared (IR) spectroscopy. The structures of newly isolated compounds, together with their anti-ESKAPE activity will be presented to assess any enhancement in potency relative to the crude extract.



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sciforum-177879: Structural Modifications of the Natural Product Gambogic Acid and Their Anticancer Activity

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Introduction

Cancer, a leading cause of death globally, arises from malignant epithelial tumors. Current clinical anticancer drugs often lack selectivity, causing significant toxicity to normal cells. Thus, developing novel, highly efficient antitumor agents with reduced side effects is a critical research priority.

Methods

To develop more efficient and less toxic antitumor agents, this study utilized gambogic acid as a lead compound and performed structural modifications at the C-30 carboxyl group based on the molecular hybridization principle. Several small molecular fragments with antitumor activity were introduced, including phenyl-1,2,3-triazole (Series A), phenyltriazolone (Series B), phenyl-1,2,4-oxadiazole (Series C), and 3-phenylisoxazole (Series D), with the aim of obtaining safer and more effective gambogic acid derivatives. The antiproliferative activities of these novel derivatives against HepG-2, A549, and HCT-116 cells were evaluated at a concentration of 10 μ M. Subsequently, selected compounds underwent further antitumor activity investigations.

Results

In this study, 30 gambogic acid derivatives were synthesized and confirmed by NMR and HRMS. Nine compounds exhibited activity when screened at 10 μ M against three cancer cell lines. Further MTT tests revealed their IC_{50} values. Series A and B derivatives were particularly effective: A4 strongly inhibited HepG-2 cells (IC_{50} = 4.69 μ M); B6 showed potent activity against A549 cells (IC_{50} = 2.72 μ M) and moderate activity against HepG-2 cells (IC_{50} = 4.82 μ M); and B1 was the most potent against HCT-116 cells (IC_{50} = 2.63 μ M), surpassing the original gambogic acid.

Molecular docking showed B1 bound strongly to the colorectal cancer target EGFR (PDB ID: 2GS2) with a binding energy of -5.849 kcal/mol, outperforming gambogic acid (-3.816 kcal/mol) and confirming its superior activity.

Conclusion

Novel gambogic acid derivatives incorporating phenyltriazolone moieties demonstrated enhanced antitumor activity. Compound B1 emerged as a promising candidate against colorectal cancer cells, meriting further investigation.



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sciforum-167596: Study of the composition of phenolic compounds and the antibacterial activity of the extract *Thymus crebrifolius* Klok

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Introduction

The increasing resistance of known pathogenic bacteria to drug therapy and the emergence of new pathogenic microorganisms are a major concern of the World Health Organization. The aim of this study was to investigate the phenolic compound composition and antibacterial activity of the extract *Thymus crebrifolius* Klok, an endemic plant of the flora of Kazakhstan.

Methods

Thymus crebrifolius grass was collected in nature and extracted with 70% ethanol using ultrasound. The composition of the extract's polyphenolic compounds was studied using LC-UV-ESI-MS/MS. The antibacterial activity of the extract was assessed by micro-dilution against 9 strains of Gram-positive bacteria, 6 strains of Gram-negative bacteria and 5 strains of fungi.

Results

According to the results of the analysis, 13 phenolic compounds were identified and quantitatively determined in the extract. The dominant compounds were cynaroside (109.00 mg/g), rosmarinic acid (30.98 mg/g), naringenin (24.84 mg/g), and apigenin-7-O-glucuronide (16.34 mg/g).

The extract exhibited the highest bactericidal activity against *Helicobacter pylori*, with MIC = 0.0625 mg/ml and MBC = 0.250 mg/ml. Bactericidal activity was observed against four Gram-positive bacterial strains (*Staphylococcus epidermidis*, *Staphylococcus aureus* ATCC 6538, *Bacillus subtilis*, *Streptococcus pneumoniae*) at concentrations of 0.313–1.25 mg/ml. In addition, the extract inhibited the growth of three strains (*Staphylococcus aureus* ATCC 25923, *Micrococcus luteus* and *Streptococcus pyogenes*) at a concentration of 1.25 mg/ml. At the same concentration (1.25 mg/ml), bactericidal activity against *Proteus mirabilis* was also observed.

Conclusion

Based on the results of studying the composition, 13 phenolic compounds were identified and quantified, including 9 flavonoids and 4 phenolic acids. It has been established that the 70% ethanol extract of *Thymus crebrifolius* can be considered as a promising substance for the development of a drug with a wide spectrum of antibacterial action and/or a parapharmaceutical agent.



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sciforum-166942: Study of the replacement of Phe and Ser with Tyr in the Temporin A molecule on the antiproliferative activity

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Introduction

Antimicrobial peptides (AMPs) are a promising candidate for multitarget therapy, since most AMPs, in addition to their antibacterial activity, also possess other properties, such as antiproliferative. This is because the mechanisms for both activities rely on electrostatic interactions between negatively charged cell membranes and positively charged peptides. Temporin A is a member of the Temporin family. It is a hydrophobic 13-amino acid long AMP with an amidated C-terminus. Research on its activity shows it is effective against Gram-positive bacteria, including strains resistant to conventional antibiotics.

Methods

Following Fmoc/Obu^t solid phase peptide strategy, two novel Temporin A analogues were synthesized. The structural modifications include the replacement of the Phe and Ser residues with Tyr in positions 1 (Y-LPLIGRVLSGIL-NH₂) and 10 (FLPLIGRVL-Y-GIL-NH₂) to examine the impact of OH-function type on the antiproliferative activity. The MTT dye reduction assay was used to test cell cultures on MCF-12F, MCF-7, and MDA-MB-231 cell lines. The cells were plated at a density of 1x10³ cells/100 µL in 96-well microplates and were left to adhere for 24 hours. Afterwards the cells were exposed to the peptides with concentrations from 4 to 1000 µM for 72 hours. Formazan absorption was measured at λ = 540 nm using a microplate reader.

Results

IC₅₀ values demonstrated antiproliferative activity. The statistical analysis used one-way ANOVA and Bonferroni's post hoc test. All results are shown as mean ± SD.

Conclusions

The introduction of an aromatic OH-group in position 1 decreased the selectivity of the analogues against the MCF-7 cell line. The two novel peptides lack effective antiproliferative activity against the MDA-MB-321 cell line.

Acknowledgments

This study is funded by the European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project N° BG-RRP-2.004-0002, "BiOrgaMCT".



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sciforum-167149: Synthesis and antiviral activity of 1-(4-pyridin-2-yl-[1,2,3]triazol-1-ylmethyl)-octahydro-quinolizine

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Introduction and Aim

A key area in medicinal chemistry is the application of synthetic transformations of the natural compounds to develop the novel and effective pharmaceutical agents. Quinolizidine alkaloids are of significant interest due to their availability and biological activity. The directed search for new therapeutic agents based on the quinolizidine alkaloid lupinine remains a critical research objective. Lupinine demonstrates the high biological activity, low toxicity and reduced side effects.

Method

Influenza A virus strains (A/H3N2 and A/H1N1) were used to assess antiviral activity. A chicken embryo model was employed to evaluate virucidal activity and its ability to inhibit viral replication.

Results and Discussion

The 1,2,3-triazole lupinine derivative was synthesized from a quinolizidine alkaloid (-)-lupinine by reacting lupinine azide with 2-ethynylpyridine under Cu(I)-catalyzed 1,3-dipolar cycloaddition conditions.

The synthesized compound 1-(4-pyridin-2-yl-[1,2,3]triazol-1-ylmethyl)-octahydro-quinolizine was found to reduce viral infectivity when applied to virus-containing material. This supports the potential for further investigation of the compound as a promising virucidal agent with activity against extracellular virions.

The composition and structure of the resulting compound were confirmed by elemental analysis, high-resolution mass spectrometry, and ¹H and ¹³C NMR spectroscopy.

Conclusion

The study proposes and develops the optimal conditions for modifying the structure of a lupinine alkaloid at the C-10 position. This modification results in the synthesis of a potentially bioactive 1,2,3-triazole derivative with high yields. The final triazole product was obtained in two stages: synthesis of the lupinine azide intermediate and its 1,3-dipolar [3+2] cycloaddition with alkyne 2-ethynylpyridine. The compound 1-(4-pyridin-2-yl-[1,2,3]triazol-1-ylmethyl)-octahydro-quinolizine demonstrates significant *in vitro* antiviral activity, as evidenced by high chemotherapeutic index values against influenza virus strains with varying antigenic properties.

The obtained results suggest that this compound is a promising candidate for further fundamental and pharmacological investigations.



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sciforum-167772: Synthesis and biological activity of novel 6-phenyl-4-azaindole derivatives

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4-Azaindoles are heterocyclic compounds structurally related to indoles, featuring a nitrogen atom substituted for a carbon at the 4-position of the benzene ring. This incorporation of a pyridine-like nitrogen alters the electronic properties of the indole scaffold, influencing acidity, basicity, and hydrogen-bonding behavior. Such structural modification often improves pharmacokinetic profiles, including solubility and metabolic stability. As a result, 4-azaindoles and their derivatives are widely investigated in medicinal chemistry and drug discovery.^{1,2}

In this research, we designed and synthesized a series of novel 6-phenyl-4-azaindole derivatives containing substituents on the phenyl ring in the *meta* or *para* position that differ in size and stereoelectronic properties, using commercially available 6-bromo-4-azaindole as starting material in the Suzuki coupling reaction. The prepared compounds were subsequently modified by alkylation of both the pyrrole and pyridine nitrogen atoms with a variety of alkyl and benzyl substituents. Synthesized compounds were characterized by infrared spectroscopy, nuclear magnetic resonance spectroscopy and high-resolution mass spectrometry. The antimicrobial activity of all prepared compounds was assessed against a representative panel of *Gram*-positive and *Gram*-negative bacteria, and their minimum inhibitory concentrations (MICs) were determined by the broth micro-dilution method. Compounds in which pyrrole and pyridine nitrogen are not alkylated showed relatively weak antimicrobial activity, while compounds containing different groups on both nitrogen atoms showed medium to strong antimicrobial activity. For selected synthesized compounds, their cytotoxic effect on selected cell lines was also evaluated.

This project is funded by The European Union – NextGenerationEU project ToSiAn (Total synthesis of bioactive metabolites – From deep sea microorganisms to new class of antibiotics and synthetic methodologies, NPOO.C3.2.R2-I1.06.0043).

References

1. Urvashi, J. B. Senthil Kumar, P. Das, V. Tandon, J. Med. Chem. 2022, 65, 6454–6495.
2. B. Lou, W. Liang, N. Jiang, Y. Guo, T. Zhang, C. Guo, T. Du, L. Huang, H. Yu, Eur. J. Med. Chem. 2025, 292, 117664



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sciforum-173748: Synthesis of 12(*R*)-Hydrazineyl-14-Deoxyandrographolide Derivatives as Potential Anticancer Agents

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Structural modification of natural products remains a powerful strategy in medicinal chemistry for the discovery of novel anticancer agents. Andrographolide, a bioactive diterpenoid lactone isolated from *Andrographis paniculata*, has attracted considerable interest due to its diverse pharmacological activities, including anti-inflammatory, antiviral, and anticancer effects. However, its moderate potency and limited structural diversity motivate the development of new derivatives with improved biological properties.

In this study, a new series of 12(*R*)-hydrazineyl-14-deoxyandrographolide derivatives was stereoselectively synthesized from andrographolide via tandem aza-conjugate addition–elimination (CAE) reactions with structurally diverse hydrazides. The reactions were conducted under mild conditions, enabling efficient functionalization at the C-12 position of the andrographolide scaffold. A variety of benzohydrazides, aliphatic hydrazides, and bis-hydrazides were successfully introduced, affording eighteen analogues in high to excellent yields (77–97%), demonstrating the robustness and versatility of this synthetic approach.

The synthesized compounds were evaluated for cytotoxic activity against a panel of human cancer cell lines, with a particular focus on neuroblastoma. Structure–activity relationship (SAR) analysis revealed that ortho-substituted benzohydrazides bearing electron-donating groups significantly enhanced cytotoxic potency. Molecular docking studies further supported the experimental findings and showed good correlation with the observed biological activity.

These results highlight C-12 hydrazine modification of the andrographolide scaffold as a promising strategy for the development of new anticancer agents.



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sciforum-167628: Synthesis of a novel bis-triazole derivative of cytisinyl-4-methyl-7-oxo-methylencoumarine

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In this study, the synthesis of a novel bis-triazole derivative of cytisinyl-4-methyl-7-oxo-methylencoumarine (1) was described. The synthesis was carried out through click chemistry reactions, specifically copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). Propargylated derivatives of 4-methylumbelliferone, alkaloid cytosine, and 1,5-diazidopentane were utilized. This approach ensured the high selectivity and reproducibility of the synthesis. The reaction was conducted in N,N-dimethylformamide, with a catalytic system of CuSO₄·5H₂O / sodium ascorbate.

In the ¹³C NMR spectrum, signals corresponding to various types of carbon atoms were recorded. A carbonyl carbon of the ester group resonated at 161.1 ppm. The oxymethylene carbon (–O–CH₂–) appeared at 62.1 ppm. The methyl group of a coumarin fragment resonated at 18.61 ppm.

The biological activity assays revealed that compound did not exhibit the radical scavenging activity against the DPPH radical. However, it demonstrated the pronounced anti-diabetic activity against α-glucosidase.

Thus, the results of this study suggested the potential of exploring the new hybrid biologically active compounds based on the natural products. Hybrid synthesis based on alkaloids and coumarins was a promising research direction, enabling the development of molecules with pronounced synergistic effects through simultaneous modulation of receptors and enzymes. Combination of multiple pharmacophores in a single molecule led to the new compounds that combined the properties of the original components.



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sciforum-176073: Synthesis of a novel bis-triazole derivative of cytisinyl-4-methyl-7-oxo-methylencoumarine

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In this study, the synthesis of a novel bis-triazole derivative of cytisinyl-4-methyl-7-oxo-methylencoumarine (1) was described. The synthesis was carried out through click chemistry reactions, specifically copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). Propargylated derivatives of 4-methylumbelliferone, alkaloid cytosine, and 1,5-diazidopentane were utilized. This approach ensured the high selectivity and reproducibility of the synthesis. The reaction was conducted in N,N-dimethylformamide, with a catalytic system of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ / sodium ascorbate.

In the ^{13}C NMR spectrum, signals corresponding to various types of carbon atoms were recorded. A carbonyl carbon of the ester group resonated at 161.1 ppm. The oxymethylene carbon ($-\text{O}-\text{CH}_2-$) appeared at 62.1 ppm. The methyl group of a coumarin fragment resonated at 18.61 ppm.

The biological activity assays revealed that compound did not exhibit the radical scavenging activity against the DPPH radical. However, it demonstrated the pronounced anti-diabetic activity against α -glucosidase.

Thus, the results of this study suggested the potential of exploring the new hybrid biologically active compounds based on the natural products. Hybrid synthesis based on alkaloids and coumarins was a promising research direction, enabling the development of molecules with pronounced synergistic effects through simultaneous modulation of receptors and enzymes. Combination of multiple pharmacophores in a single molecule led to the new compounds that combined the properties of the original components.



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sciforum-167720: Synthesis of Spiromastols

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Spiromastols are polyphenol natural products isolated from deep-sea fungi *Spiromastix* sp., that exhibit prominent bioactivity. Spiromastols A, B, C and L, structurally classified as polychlorinated diphenyl ethers, were shown to have the strongest inhibitory effect towards various bacterial strains, with minimal inhibitory concentrations ranging from 0.25 to 2 µg/mL [1], [2]. Due to their noted antimicrobial properties, they were recognised as important synthetic targets.

The converging step in the synthesis of spiromastols is the formation of an ether bond between two phenol subunits. Both subunits are synthesised using the same resorcinol derivative as the starting material. Selective protection of a single phenol group is a crucial step which allows ether formation in the proper position. Several protecting groups were considered, taking into account the feasibility of selective protecting group introduction, as well as the compatibility with the following steps and the ease of removal. Further steps include the introduction of iodide or boronic acid functionalities, which precede the formation of ether bond by either Ullman coupling or Chan-Evans-Lam coupling, respectively.

The two methodologies are investigated as distinct approaches towards the synthesis of diphenyl ether spiromastols and their efficiency is evaluated and compared. All obtained products were characterized by NMR spectroscopy and HRMS.

This project is funded by The European Union – NextGenerationEU project ToSiAn (Total synthesis of bioactive metabolites – From deep sea microorganisms to new class of antibiotics and synthetic methodologies, NPOO.C3.2.R2-I1.06.0043).

References

1. S. Niu, D. Liu, P. Proksch, Z. Shao, W. Lin, *Mar. Drugs* **2015**, *13*, 2526–2540.
2. C. Cai, Y. Chen, L. Zhou, N. Gong, H. Zhang, C. Sun, J. Ma, J. Ju, *J. Nat. Prod.* **2022**, *86*, 589–595



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sciforum-167718: Synthetic Studies Towards the Tetracyclic Core of Bromophycoic Acid E

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Marine natural products represent an inexhaustible library of diverse molecular structures and they often exhibit sought-after biological properties. Bromophycoic acids A – E are natural products isolated from Fijian red algae in the genus *Callophycus*,¹ in addition to structurally similar callophycoic acids.² Both the bromo- and callophycoic acids contain novel diterpene-benzoic acid fused molecular architectures and have prominent biological activities which include antineoplastic, anti-malarial and antibacterial properties. Despite their potential as novel therapeutics, synthetic studies towards these natural compounds are very limited. An approach towards the tricyclic core of callophycoic acid A³ is known. Additionally, a method was described for synthesis of chromones, which was shown to be applicable to the construction of the framework of bromophycoic acid E.⁴

In this research we have developed an approach to the tetracyclic core of bromophycoic acid E. The strategy enables efficient construction of the decalin framework via Robinson annulation, followed by elaboration of the obtained enone compound. Installation of the benzoic acid moiety was achieved from an advanced intermediate derived from a commercial salicylaldehyde compound. All of the obtained compounds were characterized by means of NMR spectroscopy and HRMS. Additionally, SCXRD was utilized for the determination of relative configuration of the late synthetic intermediate.

This project is funded by The European Union – NextGenerationEU project ToSiAn (Total synthesis of bioactive metabolites – From deep sea microorganisms to new class of antibiotics and synthetic methodologies NPOO.C3.2.R2-I1.06.0043).

References

1. J. Kubanek et al., J. Org. Chem. 2012, 77, 8000–8006.
2. J. Kubanek et al., J. Org. Chem. 2007, 72, 7343–7351.
3. K. Takao et al., J. Org. Chem. 2020, 85, 3245–3264.
4. B. C. Hawkins et al., J. Org. Chem. 2017, 82, 5317–5327.



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sciforum-172045: Tetrahydroxanthene-1,3(2H)-dione Dimers and Oxidized Hexadiene Derivatives from *Uvaria leptopoda*: Isolation, Structural Elucidation, and Biological Activity

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The first phytochemical investigation of the twig extract of *Uvaria leptopoda* (Annonaceae) resulted in the isolation and characterization of three new tetrahydroxanthene-1,3(2H)-diones, designated uvarialeptones A–C (1–3), together with two new oxidized hexadiene derivatives, uvarialeptols A and B (4 and 5), in addition to ten known compounds. This study expands the chemical diversity reported from the genus *Uvaria* and highlights its potential as a source of structurally intriguing polyketide-derived metabolites.

The structures of the new compounds were elucidated through comprehensive spectroscopic analyses, including 1D and 2D NMR (HSQC, HMBC, COSY, and NOESY) experiments, high-resolution electrospray ionization mass spectrometry (HRESIMS), and detailed comparison with related analogues. Notably, uvarialeptones A (1) and B (2) represent unprecedented tetrahydroxanthene-1,3(2H)-dione dimers featuring a central cyclobutane ring. Their structures suggest a biosynthetic origin via intermolecular [2 + 2] cycloaddition, likely arising from uvarialeptone C (3) and 9a-*O*-methyloxymitrone, respectively. Such dimerization leading to a cyclobutane core is rare within this class of natural products and contributes significant structural novelty. The molecular structure and absolute configuration of uvarialeptone A were unambiguously confirmed by single-crystal X-ray diffraction analysis using Mo K α radiation.

Preliminary biological evaluation revealed that compound 3 exhibited potent inhibitory activity against nitric oxide (NO) production in LPS-stimulated macrophages, with an IC₅₀ value of 6.7 ± 0.1 μ M, without significant cytotoxicity at active concentrations. These findings indicate promising anti-inflammatory potential and underscore the relevance of tetrahydroxanthene-1,3(2H)-dione derivatives as bioactive scaffolds. Overall, this study provides new insights into the chemical diversity and biological significance of secondary metabolites from *U. leptopoda*.



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sciforum-180700: Transcriptomic Insights into the Anti-Aging Mechanisms of Picroside I: Metabolic Reprogramming and Cellular Defense in *C. elegans*

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Aging is a universal and irreversible physiological process. This study utilizes *Caenorhabditis elegans* as a model organism to systematically evaluate the anti-aging activity of the natural product Picroside I and explore its underlying molecular network mechanisms. Physiological experiments demonstrate that a 10 μ M Picroside I intervention significantly extends the healthspan and enhances the muscle vitality of the nematodes. Furthermore, high-concentration interventions substantially reduce the accumulation of advanced glycation end products (AGEs) and lipofuscin in the intestine. To elucidate the underlying mechanisms, transcriptomic analyses (GO and KEGG) reveal that Picroside I systematically regulates global metabolic pathways. The compound extensively downregulates basal energy metabolism pathways and ribosomal structural genes, inducing a physiological protective state characterized by reduced metabolic consumption. Concurrently, it significantly inhibits arachidonic acid metabolism and various stress response pathways, blocking the chronic inflammatory responses associated with aging at the metabolic source. Conversely, Picroside I significantly upregulates glycosyltransferase activity in the endoplasmic reticulum and Golgi apparatus, thereby improving the modification quality and structural stability of nascent proteins. In addition, it highly activates the functions of lysosomes, peroxisomes, and ABC transporters, greatly enhancing the cellular capacity for the efflux and degradation of metabolic waste and toxic substances. In conclusion, Picroside I exerts its anti-aging effects through a multidimensional synergistic mechanism that reduces overall metabolic load, inhibits chronic inflammation, and strengthens cellular defense and waste clearance systems. This study provides an experimental basis for Picroside I in extending healthspan and offers a new scientific perspective for the application of active small molecules from traditional Chinese medicine in intervening against aging and degenerative diseases.



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sciforum-169309: Triptolide Enhances Valve Interstitial Cell Autophagy-Lysosomal Function to Alleviate Calcific Aortic Valve Disease

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Introduction

Calcific aortic valve disease (CAVD) is a serious valvular condition with increasing prevalence, posing a significant threat to patient health. Currently, no effective pharmacological treatment is available, leaving transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) as the only clinical options, which impose substantial physical and economic burdens. Osteogenic differentiation of valvular interstitial cells (VICs) represents a key pathological process in CAVD, where autophagy-lysosome dysfunction impedes proteolytic clearance of osteogenic drivers such as ALP and RUNX2, thereby promoting calcification. This study seeks to elucidate the regulatory role of the autophagy-lysosomal pathway in VICs osteogenesis and assess the therapeutic potential of the Triptolide in suppressing this process.

Methods

An ELISA-based high-throughput screening of over 900 natural compounds identified inhibitors of VICs osteogenic differentiation. Integrated strategies, limited proteolysis mass spectrometry (LiP-MS), drug affinity responsive target stability (DARTS), cellular thermal shift assay (CETSA), molecular docking, dynamics simulations and surface plasmon resonance (SPR), elucidated direct interaction between Triptolide and CTSD. siRNA knockdown and overexpression functionally validated CTSD and lysosomal roles in osteogenesis. Triptolide's anti-calcification efficacy was further validated in an ApoE^{-/-} mouse CAVD model.

Results

High-throughput screening identified Triptolide as the most potent inhibitor of VICs osteogenic differentiation, exhibiting notable dose-dependent efficacy. Mechanistic investigation revealed that Triptolide by directly targeting CTSD to promote its maturation and activity as well as modulating the mTOR/AKT/TFEB signaling axis to enhance lysosomal degradation capacity, ultimately augments autophagic flux in VICs, thereby suppressing osteogenic differentiation and calcified nodule formation. In vivo, Triptolide treatment significantly improved hemodynamic performance, reduced valve thickness and calcified nodule formation, and suppressed the expression of key osteogenic genes.

Conclusion

In summary, our findings highlight Triptolide as a promising therapeutic candidate for CAVD treatment and reveal, for the first time, the lysosome and CTSD as potential therapeutic targets for CAVD.



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Session 4. AI for Drug Discovery

sciforum-161758: *De Novo* Design of Anti-Aging Peptides

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Aging, a universal biological process in complex organisms, is increasingly recognized to be driven by progressive loss of epigenetic information, as proposed in the Information Theory of Aging (ITOA). However, research on anti-aging peptides remains scarce, with most existing efforts confined to derivatives of natural proteins, while systematic design attempts are virtually absent. This limitation not only restricts discovery within the evolutionary sequence space but also hampers the identification of candidates with novel mechanisms and improved efficacy. *De novo* design does not rely on any known protein templates, thereby enabling exploration of a vastly broader sequence and structural space, which may yield entirely novel peptides not found in nature. In this study, guided by the ITOA, we present ElixirSeeker2, a novel framework for *de novo* design of anti-aging peptides. Our approach integrates modeling of existing anti-aging peptides, activity scoring using the IC50 database, and penalty terms from toxic peptide datasets to enforce safety constraints. ElixirSeeker2 enables large-scale virtual screening and identification of novel peptide candidates. Several lead peptides demonstrated significant effects in delaying cellular senescence, restoring cellular functions in vitro and in enhancing locomotor activity of aged *Caenorhabditis elegans*. Importantly, this work not only provides a collection of entirely new anti-aging peptide candidates but also validates the feasibility and great potential of *de novo* design as a paradigm-shifting strategy for the development of anti-aging biologics.



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sciform-166688: Trillion Ligands per Day: Performance-Portable Virtual Screening via Compound Database Optimization and Multi-Target Docking

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Structure-based virtual screening (SBVS) confronts a grand and pressing challenge in scaling to ultra-large compound libraries, a bottleneck that severely restricts the efficiency of novel drug discovery campaigns targeting diverse disease-related targets. Herein, we present SWDOCKP², a high-performance and portable virtual screening framework that achieves an unprecedented throughput of 1.9 trillion ligand-receptor binding predictions daily across eight distinct protein targets on the Sunway OceanLight supercomputer with 39-million processing cores—representing a 10× speedup over the prior state-of-the-art methodologies. Three key synergistic innovations underpin this breakthrough: (1) a ligand database optimizer integrated with conformational sorting and merging to streamline data preprocessing and reduce redundancy; (2) multi-receptor grid alignment that enables parallelized multi-target screening and leverages SIMD-accelerated trilinear interpolation for fast and accurate binding affinity estimation; and (3) a Sunway architecture emulator to ensure cross-platform compatibility and efficiency across heterogeneous computing environments. These advancements effectively bridge the gap between extreme computational scalability and the growing demands of modern drug discovery, offering a robust blueprint for next-generation supercomputing-driven SBVS. Additionally, SWDOCKP² is poised to generate an unprecedented large-scale dataset of predicted protein-ligand interactions, a transformative resource that addresses the long-standing experimental data scarcity bottleneck and empowers the development of accurate ligand prediction models, generative chemistry algorithms, and AI-driven drug discovery pipelines.



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sciforum-178100: Accelerating FIC Drug Discovery via a Self-Optimizing Pharmacophore-Based Molecular Generative Model

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Introduction

Pharmacophore-guided molecular generation offers a promising approach for novel drug design by incorporating interaction constraints that accommodate target flexibility. However, current methods rely heavily on accurate initial pharmacophore models, which are often unavailable for understudied or novel targets. This limitation hinders their application in first-in-class drug discovery, where only crude pharmacophore hypotheses can be constructed.

Methods

We propose a novel iterative optimization strategy that decouples pharmacophore refinement from molecular generation. A pharmacophore optimization model was developed by learning from pharmacophore models derived from known and simulated protein-ligand complexes. The model iteratively refines initial pharmacophore hypotheses through feature addition, deletion, and substitution operations guided by Monte Carlo tree search, enabling asynchronous co-evolution of pharmacophore models and molecular structures without requiring accurate starting hypotheses.

Results

The constructed dataset, comprising 14+ million pharmacophore models and 260,000+ drug-like molecules, provides a comprehensive foundation for learning transferable optimization strategies. Preliminary validation across 12 test systems demonstrated statistically significant improvements in docking scores for 10 systems, with generated molecules forming enhanced and anticipated interactions with target proteins. A proof-of-concept study on the FPR2 receptor showed that iterative pharmacophore optimization combined with molecular generation successfully guided the discovery of highly potent ligands.

Conclusions

This work establishes a generalizable framework that transforms pharmacophore-guided molecular generation from accurate hypothesis-dependent to error-tolerant scenarios. The approach holds promise for accelerating drug discovery against challenging targets and may extend to broader biomolecular interaction design problems, including protein-protein interaction modulators and antibody epitope optimization.



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sciforum-165635: Machine Learning Approaches for Predicting ADMET Parameters in Drug Development: Integrating Molecular Descriptors and Deep Learning

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The pharmaceutical industry is confronted with mounting costs and time constraints in the process of drug discovery, underscoring the imperative for effective early-stage ADMET evaluation. The present work was aimed in developing computational models through machine learning (ML) and deep learning (DL) to predict key pharmacokinetic parameters.

A comprehensive compilation of datasets pertaining to various parameters was conducted, encompassing the fraction unbound (fu), the volume of distribution (VD), the half-life, major cytochrome P450 interactions (1A2, 2C9, 2C19, 2D6, and 3A4), and hepatic/renal clearance. The data underwent a thorough cleaning and curation process. Molecular features were extracted using RDKit and PaDEL, which generated molecular descriptors and Morgan fingerprints.

For machine learning (ML), algorithms such as gradient boosting (GB) and random forest (RF) were employed. The models were trained, optimized, and validated on independent external test sets. The findings demonstrated the efficacy of VD (r^2 (fit)=0.99, q^2 (test)=0.71, r^2_{pred} (validation)=0.66) and CYP interactions (MCC_{pred} (validation) CYP1A2=0.70, CYP2C9=0.60, CYP2C19=0.63). The fu prediction ability exhibited a slightly lower robustness (r^2_{pred} (validation)=0.54). The classification models for half-life demonstrated moderate performance, as indicated by an F1-macro (validation) value of 0.55.

In addition, the potential of deep learning (DL) models, such as multi-layer perceptrons and graph neural networks, to capture complex, non-linear structure-property relationships in ADMET prediction was investigated. The objective of this study was to establish a correlation between the predicted parameters and the clearance mechanisms.

The application of both machine learning (ML) and deep learning (DL) approaches has been demonstrated to hold considerable promise for the early prediction of ADMET properties. These approaches offer tools that can facilitate the optimization of compounds and the reduction of late-stage failures, thereby contributing to the streamlining of drug development processes.



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sciforum-182843: An AI-Driven Pipeline for the Discovery of Novel Advanced Glycation End-Product Inhibitors

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Advanced glycation end-products (AGEs) are important pathological drivers of biological ageing and multiple chronic diseases, including diabetes, cardiovascular disorders, and neurodegeneration. However, the discovery of effective AGE inhibitors remains challenging because conventional screening approaches are costly, time-consuming, and inefficient in data-sparse therapeutic areas. In this study, we established an artificial intelligence-enabled pipeline for the discovery and validation of novel AGE inhibitors. A curated AGE-inhibitor dataset was constructed through systematic literature and patent mining, and molecular structures were encoded using a pretrained chemical-language Transformer to generate 768-dimensional embeddings. Multiple machine-learning models were benchmarked using nested cross-validation, and Random Forest was selected as the best-performing classifier for large-scale virtual screening of the ChEMBL database. Top-ranked compounds were further evaluated by quantum-chemical calculations, molecular docking, molecular dynamics simulations, in vitro AGE inhibition assays, and in vivo validation in a *Caenorhabditis elegans* glycation model. Random Forest showed the strongest predictive performance among the tested models and was used to screen more than 2 million compounds, leading to the prioritization of five purchasable natural-product candidates for experimental testing. Computational analyses supported their potential relevance to glycation-related mechanisms. In vitro assays demonstrated that all five compounds significantly inhibited AGE formation in a dose-dependent manner, and all candidates also significantly reduced AGE accumulation in glycation-induced *C. elegans* in vivo. Together, these findings identify novel AGE-inhibitory lead compounds and establish an efficient and scalable AI-driven discovery pipeline integrating virtual screening, molecular simulation, and biological validation for anti-glycation drug discovery.



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sciforum-167489: AI-Assisted Integration of Molecular Networking, Bioactivity Data, and *In Silico* Modeling for Natural Product Drug Discovery: Case Studies of Medicinal Plants in Vietnam

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Medicinal plants constitute chemically complex matrices that pose significant challenges for conventional drug discovery approaches based on single-compound isolation. Recent advances in artificial intelligence-enabled data analytics, particularly molecular networking and bioactivity-informed modeling, provide new opportunities to translate complex metabolomic data into actionable knowledge for drug discovery. This presentation highlights an AI-assisted workflow that integrates chemical profiling, bioactivity-based molecular networking (BBMN), and *in silico* target prediction to support early-stage natural product-based drug discovery. Untargeted UHPLC–HRMS/MS datasets were processed through feature-based molecular networking on the GNPS platform to visualize chemical relationships and prioritize metabolite families. Bioactivity-based molecular networking was subsequently applied by integrating LC–MS/MS features with cytotoxicity data, enabling data-driven identification of metabolite clusters most strongly associated with biological effects. In parallel, *in silico* target prediction using SwissTargetPrediction was employed to infer putative mechanisms of action and support hypothesis generation. The workflow is illustrated through two case studies of Vietnamese medicinal plants, *Cibotium barometz* and *Sesbania grandiflora*. In *C. barometz*, molecular networking revealed glycolipids and phenolic derivatives as major chemical classes, while AI-assisted target prediction suggested interactions with inflammation- and tissue-repair-related proteins, providing mechanistic insight into traditional therapeutic uses and highlighting additional drug-relevant targets. In *S. grandiflora*, BBMN integrating metabolomic features with cytotoxicity assays against A549 and HepG2 cell lines identified triterpenoid aglycones and saponins as the principal contributors to anticancer activity. This network-guided prioritization enabled focused isolation and experimental validation of representative bioactive compounds. Overall, this work illustrates how AI-assisted molecular networking, bioactivity-based molecular networking, and *in silico* target prediction can enhance compound prioritization and mechanism-oriented interpretation in natural product drug discovery. By converting high-dimensional metabolomic and bioactivity datasets into interpretable molecular networks, this integrative framework connects traditional medicinal knowledge with contemporary AI-driven discovery strategies.



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sciforum-167777: Assessment of affinity prediction approaches in small molecular drug discovery

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Improving the potency of lead molecules is crucial in drug discovery, as it determines therapeutic efficacy, clinical dosage, and therapeutic windows. Before chemical synthesis, utilizing computational methods for accurate and high-throughput potency prediction can significantly accelerate the drug optimization process. Currently, from a methodological perspective, this field is categorized into physics-based approaches and data-driven (AI/ML) methods. These applications are available as both commercial software and open-source tools. Herein, we provide a systematic evaluation and analysis of different methodologies and demonstrate the influence of key computational parameters. Our findings indicate that while the performance of various methods varies across different systems, physics-based free energy prediction (FEP) generally demonstrates high accuracy in most cases, compared with QM/MD-based approaches and AI/ML models. Two FEP platforms are compared in detail: an open-source protocol from the Open Free Energy (OpenFE) ecosystem and the commercial FEP+ module from the software company Schrodinger. Performance was found to be more dependent on the protein targets and ligand transformation types, rather than the software used. Importantly, the domain of applicability is also different between the two methods. We also show how FEP+ was prospectively applied in a real-world drug discovery project to accelerate the compound optimization cycle.



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sciforum-164942: Fragment-Based Diffusion Modeling and Molecular Dynamics Simulation Validation for the Discovery of PD-L1 Small-Molecule Inhibitors

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The programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) immune checkpoint pathway plays a critical role in tumor immune evasion and has become a major target in cancer immunotherapy. Although monoclonal antibodies (mAbs) targeting the PD-1/PD-L1 axis have demonstrated remarkable clinical efficacy, their application is limited by poor tissue penetration and high production costs. Consequently, the discovery of small-molecule inhibitors that disrupt the PD-1/PD-L1 interaction has attracted increasing attention. Previous studies have reported that certain small-molecule inhibitors can induce PD-L1 dimerization, thereby effectively blocking PD-1/PD-L1 binding. In parallel, diffusion models have recently been widely applied in fragment-based drug design (FBDD) due to their capability to generate structurally reasonable molecules with high conformational quality. Based on the reported co-crystal structures of PD-L1/small-molecule inhibitor complex and diffusion models, the development of novel PD-L1 small-molecule inhibitors via fragment-based diffusion modeling strategy has become feasible. In this work, we utilized diffusion model, molecular docking and molecular dynamics (MD) simulation to discover novel PD-L1 small-molecule inhibitors. A total of 455 novel molecules were generated from 7 PD-L1/small-molecule inhibitor complex co-crystal structures, of which 199 chemically reasonable compounds were retained for docking-based screening. Subsequently, 5 top-ranked compounds were subjected to 500 ns MD simulation. One compound was excluded due to lack of convergence, while the remaining four candidates (denoted as bo1-bo4) were further evaluated. The analysis of binding free energy (BFE) and MD simulation validation indicates that 3 compounds (bo1, bo2, and bo3), exhibiting BFE lower than -40 kcal/mol, show strong potential as PD-L1 inhibitors. Overall, this work demonstrates that FBDD-guided diffusion modeling provides a computationally efficient and robust strategy for small-molecule inhibitor discovery, providing a promising framework for tackling challenging targets in cancer immunotherapy.



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sciforum-167332: Integrating HPC and AI to Advance Protein–ligand Binding Interaction Prediction

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In small-molecule drug discovery, accurate and efficient prediction of protein–ligand interactions is essential for identifying leads for new targets, yet current AI models are limited by the lack of large, high-quality structural and binding data, which restricts their generalization in real-world settings. Physics-based high-performance computing (HPC) helps overcome this limitation by generating large, high-fidelity datasets for training and validating advanced AI models, enabling exploration of molecular interaction space at unprecedented scale.

Leveraging this paradigm, BindingNet v2 was constructed as an extensively expanded dataset of 689,796 modeled protein–ligand complexes across 1,794 protein targets, built via an enhanced template-based workflow from BindingNet v1 that integrates advanced pharmacophore and molecular shape similarity methods to improve binding mode prediction. When used to augment the PDBbind dataset, BindingNet v2 markedly improved the Uni-Mol model's pose prediction performance on the challenging PoseBusters benchmark, increasing the success rate from 38.55% to 64.25%, underscoring the importance of large, diverse datasets for robust AI in drug discovery.

Additionally, machine learning interatomic potentials (MLIPs) enable quantum-level molecular modeling but require robust training data. PANIP, an ensemble model built on NequIP, uses a multi-fidelity active learning workflow to extract diverse, information-rich subsets, focusing expensive QM calculations on key structures. Trained on non-covalent protein interactions, PANIP compresses data to 8.7% while maintaining accuracy (MAE 0.2 kcal/mol). It outperforms ANI-2x, generalizes well to biomolecular systems, and achieves near-force-field speed with QM precision.

More broadly, the integration of HPC and AI is enabling more accurate and efficient calculations of molecular interactions, offering a path to systematically address data scarcity and enhance predictive power. As AI architectures are increasingly co-designed for HPC environments, molecular interaction predictions can be performed more rapidly and at lower cost, promising to accelerate drug discovery timelines, reduce development expenses, and deliver new therapies to patients more quickly and effectively.



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sciforum-166509: Large-Scale Screening of PD-L1 Small-Molecule Inhibitors via Integration of AI Models and Molecular Dynamics Simulations

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Over the past decade, numerous monoclonal antibodies targeting programmed cell death ligand-1 (PD-L1) have been approved to block the programmed cell death-1 (PD-1)/PD-L1 immune checkpoint pathway. Inhibition of this pathway has proven to be an effective strategy for activating antitumor immune responses. However, antibody-based therapeutics suffer from several limitations, including poor tumor penetration, high production costs, and immune-related adverse events. In recent years, increasing evidence has shown that small-molecule inhibitors can suppress the PD-1/PD-L1 pathway by inducing PD-L1 dimerization. To identify potential lead compounds targeting PD-L1, we performed a large-scale computational screening integrating bioactivity prediction, ADMET profiling, and free energy perturbation (FEP) calculations. A fused dataset of approximately three million compounds assembled from the ZINC, ChEMBL, and BindingDB databases was initially filtered using the Lipinski rule of five and the Veber rule, followed by screening with an ensemble prediction model, gnina, ADMETlab 3.0, admetSAR 3.0, and ADMET-AI. As a result, two candidate molecules, ChEMBL1642757 and ChEMBL5907171, were selected for further analysis. FEP calculations revealed binding free energies of -10.02 and -8.65 kcal/mol for these compounds, respectively, indicating strong binding affinities toward PD-L1. These results suggest that the identified molecules represent promising PD-L1 inhibitor candidates. Experimental validation of their bioactivity is currently ongoing.



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sciforum-166848: LMPep: An LLM-Guided Genetic Algorithm for De Novo Design of High-Affinity Therapeutic Peptide Sequences

Yi Yang *, Xinying Zhu, Jie Yue, Jing Zhang and Yonggang Wei

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Therapeutic peptides represent a critical modality in modern drug discovery, yet designing sequences with high binding affinity remains a challenge. In recent years, large language models (LLMs) such as ChatGPT have demonstrated extraordinary capabilities. Here, we present **LMPep**, a framework that integrates an LLM with a genetic algorithm (GA) to enable *de novo* design of high-affinity peptide sequences. In LMPep, the LLM functions as an **intelligent evolutionary operator**, selecting mutation candidates and crossover sites based on LLM chemical intuition. Crucially, we employ in-context learning to construct the LLM's memory, allowing it to learn from the evolutionary history of high-fitness individuals and propagate beneficial sequence motifs across generations. We further evaluated multiple LLMs within LMPep to characterize how model choice affects the evolutionary search efficiency and the quality of the optimized peptides. To guide the optimization toward potent binders, we utilize BindPred, a protein-protein binding affinity predictor based on ESMFold embeddings, as the fitness function to minimize the predicted dissociation constant. We extensively benchmarked LMPep against state-of-the-art diffusion models and Variational Autoencoders (VAEs). The extensive experiments demonstrated that LMPep not only generates sequences with high novelty and diversity but, more importantly, consistently yields candidates with significantly improved predicted binding affinities compared to baselines. Overall, LMPep demonstrates that integrating LLM-guided operators with evolutionary search provides an effective and general strategy for navigating peptide chemical space toward therapeutically relevant, high-affinity sequences.



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sciforum-166062: Predicting drug delivery systems via quantum chemistry data-driven machine learning

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All-boron fullerene B₄₀ with distinct structural and electronic features exhibits great potential as a novel drug carrier. In this study, a model named “**AI-B₄₀Screen**” was developed based on the quantum chemistry calculations and machine learning algorithms to predict the adsorption energy (E_{ad}) of small-molecule drugs onto B₄₀. Firstly, the training set and independent test set were constructed by calculating the E_{ad} values of 70 ring-structures/pharmacophores of drugs onto B₄₀ and 53 descriptors of each ring/pharmacophore structure via density functional Theory (DFT). The proposed model demonstrates excellent performance on the validation set (Pearson $r = 0.975$, RMSE = 0.087) and maintains strong predictive accuracy on an independent test set (Pearson $r = 0.905$, RMSE = 0.206). Then, a data set containing 53 descriptors of 1545 FDA-approved small-molecule drugs have been constructed via DFT calculations. So, the E_{ad} values of these drugs onto B₄₀ have been systematically predicted via the **AI-B₄₀Screen** model. To validate the reliability of this model, 10 drugs were randomly selected to calculate their E_{ad} values onto B₄₀ by DFT, which shows strong agreement with the model-predicted results. Our results confirm the predictive precision and practical utility of the proposed AI-aided model. Consequently, this study provides an efficient and reliable data-driven machine learning strategy for exploring molecular drugs suitable for the delivery by a certain material carrier, such as B₄₀, and thus offers new insights for the high-throughput computational screening of drug delivery systems.



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sciforum-166510: Predictive modeling and mechanistic validation of synergistic pimodivir combinations for anti-influenza therapy via PB2cap affinity boost

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Influenza A virus (IAV), a segmented negative-sense RNA virus in the *Orthomyxoviridae* family, causes seasonal epidemics and pandemics with substantial public health burdens. Frequent antigenic drift and reassortment drive the emergence of novel strains, complicating prevention and treatment. The rapid discovery of synergistic antiviral combinations remains a critical challenge in combating virus diseases. Antiviral drug development strategies include novel drug creation, drug repurpose, and synergistic combination therapies. Synergistic combinations are particularly valuable for addressing cross-resistance, as demonstrated by oseltamivir-zanamivir therapy effectively inhibiting drug-resistant H1N1 strains. Here, we present a machine learning (ML) framework integrating drug characterization and cellular activity data to predict efficacious single and combinatorial therapies against influenza A. Our model identified pimodivir—a PB2 cap-binding inhibitor—paired with epinephrine bitartrate or L-adrenaline as top candidates, demonstrating broad-spectrum synergy against pandemic H1N1 and recent circulating bovine H5N1 viruses. Experimental validation revealed these combinations enhance pimodivir's binding affinity to the PB2cap domain. Minigenome assays confirmed dose-dependent synergistic suppression of viral polymerase activity, despite neither adjuvant showing standalone efficacy. Multi-model synergy scoring methods (ZIP, Loewe, HSA, Bliss) and cytopathic effect profiling further validated the therapeutic potential of the selected drug combinations. Our findings offer a roadmap for rational combination therapy design against influenza and potential other RNA viruses.



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sciforum-167318: Proteome-wide large scale docking for ligand discovery

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Structure-based docking is a key strategy in drug discovery, yet single-target workflows limit efficiency and often overlook off-target interactions. Despite the size of the human proteome, only 704 of the 20,412 annotated protein targets currently have known small-molecule drugs, leaving the vast majority unexplored. Proteome-wide docking offers a scalable route for novel ligand discovery, target profiling, and off-target assessment, but its computational cost has long been prohibitive. Recent advances in SWDOCK and SWDOCKP², achieving trillion-scale throughput, now make large-scale proteome docking feasible.

In this study, we present one of the first practical implementations of proteome-wide large-scale docking. We constructed a high-quality pocket database covering ~78% of human proteins and stratified binding sites by ligandability confidence into holo, holo-like, and apo classes. High-quality pockets were prioritized by rigorous quality filters followed by repair and optimization. Using SWDOCK on the Sunway supercomputer, we docked a 1.5-million-compound library against ~15,000 pocket structures, incorporating multiple receptor conformations for dynamic proteins. This campaign generated ~22.5 billion protein–ligand evaluations. The dataset enabled the identification of novel DRD1 ligands, revealed drug-repurposing opportunities, and captured complex polypharmacology patterns. It also provides broad coverage for analyzing physicochemical interaction features across the proteome.

Overall, this work establishes a scalable framework for proteome-wide structure-based discovery. The resulting datasets offer a panoramic view of protein networks derived from structures and predicted ligands, supporting novel ligand discovery, off-target prediction, and drug-repurposing opportunities. Moreover, the dataset's scale and diversity offer a rich foundation for training advanced AI models in protein–ligand interactions.



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sciforum-180692: Virtual Screening and Validation of Small-Molecule Inhibitors Targeting Early A β Aggregation in Alzheimer's Disease

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Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, and the abnormal aggregation of A β into oligomers and fibrils is a key pathological factor leading to synaptic toxicity and cognitive impairment. The use of antibody drugs such as Lecanemab is limited due to their low blood-brain barrier permeability, significant side effects, and high cost. The development of small-molecule inhibitors capable of crossing the blood-brain barrier and intervening in early A β aggregation is of great significance. The structures of A β β -hairpins and short fibrils resolved in 2024 provide key targets for small-molecule drug design.

This study established a target system covering six representative early-stage A β conformations (β -hairpin monomers/oligomers and short fibrils). Using Karmadock to perform a large-scale virtual screening of the ChEMBL34 database (approximately 2.4 million compounds) (nearly 29 million docking simulations). Through multi-stage intersection screening, machine learning-based blood-brain barrier (BBB) permeability prediction, and anti-aging model evaluation, candidate compounds were optimized and validated via molecular dynamics simulations and the *Caenorhabditis elegans* (*C. elegans*) CL4176 model.

Following TOP 1% screening and BBB prediction, 942 candidate compounds were identified, ultimately narrowing down to two commercially available natural products—Guanosine 5'-diphospho-beta-L-fucose sodium salt (GDP-L-fucose) and Corilagin. Molecular dynamics simulations revealed that GDP-L-fucose locks A β monomers in an anti-aggregative state and stabilizes hexamers through “conformational constraints” and “energy barrier elevation”; Corilagin, on the other hand, increases the conformational diversity of A β monomers, stabilizing them in a non-pathogenic state. *C. elegans* experiments confirmed that both compounds significantly delayed A β -induced paralysis phenotypes and exerted neuroprotective effects.

The AI-assisted multi-conformation virtual screening strategy established in this study can efficiently identify small-molecule inhibitors targeting early A β aggregation, providing new candidate compounds and a theoretical framework for early intervention in AD.



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Session 5. Drug Discovery Targeting GPCRs and Ion Channels

sciforum-181363: Selective Targeting of ATP-Sensitive Potassium Channels: Structure-Based Discovery of Kir6.1/SUR2B Subtype-Selective Inhibitors

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Introduction

ATP-sensitive potassium (KATP) channels composed of Kir6.x and SUR subunits play a central role in coupling cellular metabolism to membrane excitability. In particular, Kir6.1/SUR2B channels are critical regulators of vascular tone, blood flow, and blood pressure and have been implicated in cardiovascular disorders [PMID: 35876283], Cantú syndrome [PMID: 37527933], migraine [PMID: 37456521], and diseases of the female reproductive system [PMID: 32838485]. Despite their therapeutic relevance, the development of selective Kir6.1/SUR2B inhibitors remains challenging due to high homology with other KATP channel subtypes, notably Kir6.2/SUR1.

Methods

We hypothesized that subtype selectivity is driven by interactions with specific residues within the SUR2B subunit, particularly Y1205. Ligand-protein docking was performed using SiteMap-guided constraints to evaluate binding preferences of known inhibitors toward Kir6.1/SUR2B versus Kir6.2/SUR1. Guided by these insights, a combinatorial library of analogs based on the selective inhibitor VU0542270 was designed and synthesized, focusing on systematic modifications of the left-hand side of the urea linker while preserving key features of the thiophene moiety. Docking and *in silico* ADMET profiling were applied to all synthesized compounds.

Results

VU0542270 and its analogs displayed stronger predicted binding to Kir6.1/SUR2B compared to Kir6.2/SUR1, supporting residue-specific selectivity. Docking studies of 152 synthesized compounds revealed improved Kir6.1/SUR2B binding relative to the parent molecule, with 120 analogs showing favorable predicted ADMET properties. Among these, 70 compounds met key pharmacokinetic criteria, and 40 exhibited docking scores below -6. The most potent analogs featured a substituted pyrrolidine-2-one moiety, with R-configuration conferring enhanced binding affinity.

Conclusions

These results define key structural and stereochemical determinants of Kir6.1/SUR2B selectivity and provide a rational framework for the development of novel, subtype-selective KATP channel inhibitors with therapeutic potential.



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sciforum-167679: CB₂ receptor as a GPCR-Based Therapeutic Target in the ALS/FTD Spectrum

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) constitute a pathological continuum characterized by progressive motor and cognitive impairment driven by early neuronal degeneration. Increasing evidence indicates that maladaptive activation of glial cells and sustained neuroinflammation critically contribute to neuronal vulnerability in both disorders, identifying glial signaling pathways as attractive targets for disease-modifying therapies. In this context, the cannabinoid receptor type 2 (CB₂), a G protein-coupled receptor (GPCR) markedly upregulated in activated microglia and astrocytes, has emerged as a promising therapeutic target due to its regulatory role in glial proliferation, cytokine release, and migration-related processes.

Here, we investigated the therapeutic relevance of CB₂ receptor using complementary pharmacological and genetic approaches in two transgenic TDP-43-based mouse models that recapitulate key pathological features of ALS (Prp-hTDP-43(A315T)) and FTD (CaMKII-TDP-43). Chronic administration of the selective CB₂ agonist HU-308 in the ALS model significantly attenuated microglial activation, as evidenced by reduced Iba-1 immunoreactivity, decreased soma volume, and increased branching complexity, leading to improved preservation of motor neurons and a delayed onset of motor symptoms. In the FTD model, HU-308 reduced gliosis by limiting glial recruitment to affected regions, with prominent effects on microglia in the medial prefrontal cortex and hippocampus, and a more region-restricted impact on astrocytes within the hippocampal CA1 subfield. These glial-modulatory effects were associated with enhanced neuronal survival and improved cognitive performance.

In addition, genetic ablation of the CB₂ receptor in the ALS model accelerated symptom onset and exacerbated microgliosis and astrogliosis, providing direct functional evidence for a protective role of endogenous CB₂ signaling during disease progression. Overall, our results demonstrate that CB₂ critically modulates neuroinflammatory responses and neuronal survival in the ALS/FTD spectrum, supporting its targeting for the development of disease-modifying therapies in neurodegenerative disorders.



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sciforum-167743: Discovery of Novel Adenosine A2AR/A2BR Dual Antagonists for Cancer Immunotherapy

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As a new generation of immune checkpoints, adenosine A2AR and A2BR have been considered as novel drug targets for small molecule cancer immunotherapy. A2AR and A2BR are often co-expressed on immune cells and jointly mediate tumor immune escape. A2BR is also expressed on tumor cells, complementarily promoting cancer progression. A2AR/A2BR dual antagonists demonstrate significant therapeutic advantages compared to single-target antagonists. The majority of reported dual antagonists exhibit stronger activity against A2AR than A2BR, demonstrating suboptimal balance between these two receptor subtypes. Furthermore, there remains a lack of systematic understanding of the structure-activity relationship (SAR) regarding the selective antagonism between A2AR and A2BR. Building upon our research group's preliminary discovery that structural fine-tuning can modulate the selectivity ratio between A2AR and A2BR, we focuses on the design and synthesis of novel pyrimidine derivatives guided by the co-crystal structure of AB928-A2AR complex resolved by our collaborators. Through comprehensive studies on the SAR, binding modes, anti-tumor efficacy and immunomodulatory mechanisms, novel A2AR/A2BR dual antagonists with high activity and balanced selectivity, favorable drug-like properties, and promising in vivo efficacy were discovered and evaluated for their potential uses in cancer immunotherapy. These studies validate the therapeutic advantages of enhanced A2AR and A2BR activity and balanced selectivity in anti-tumor efficacy.



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sciforum-170102: Photocrosslinking-assisted platform for GPCR deorphanization and related drug discovery

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G protein-coupled receptors (GPCRs) constitute a major family of transmembrane proteins that transduce extracellular stimuli into intracellular signals, playing central roles in virtually all physiological processes and are the most successful drug targets. The identity and function of GPCRs are largely determined by their ligands, yet approximately one hundred non-olfactory GPCRs remain orphan, with no identified endogenous ligands. Here we establish a chemical biology approach for GPCR deorphanization by site-specifically incorporating the photocrosslinker DiZPK into receptors, to capture and enrich endogenous ligands under native biological conditions in a temporally controlled and interface-selective manner. Using known GPCR–ligand pairs, we systematically validate the sensitivity, specificity, and scalability of this platform. Applying this strategy, we identify the neuropeptide Little-LEN (L-LEN) from the mouse hypothalamus as the endogenous ligand for GPR50. L-LEN selectively binds GPR50 and triggers downstream Gi signaling, and modulates cellular activity through endogenous receptors in tissues. Moreover, L-LEN and GPR50 function coordinately as a ligand–receptor pair in mice in vivo, as evidenced by shared phenotypes resulting from L-LEN or GPR50 deficiency and by the requirement of both ligand and receptor for metabolic regulation in vivo through brain–adipose tissue crosstalk. Together, these results establish a sensitive and generalizable platform for ligand–receptor pairing in native and complex biological samples, and the deorphanization of GPR50 highlights new opportunities for physiological regulation and therapeutic discovery.



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sciforum-165082: Psychedelics-inspired drug discovery: structure-based design of subtype-selective 5-HT_{2A} agonists

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Classical psychedelics are defined as serotonergic hallucinogens that induce visual hallucinations primarily through activation of the serotonin 2A receptor (5-HT_{2A}R), a class A G protein-coupled receptor (GPCR). Psychedelic compounds such as psilocybin, LSD and 5-MeO-DMT have demonstrated promising therapeutic effects for the treatment of neuropsychiatric diseases, for example treatment-resistant depression. Importantly, the antidepressant effects of psychedelics appear to be rapid and long-lasting compared to traditional selective serotonin reuptake inhibitors (SSRIs). However, their concurrent activation of the serotonin 2B receptor (5-HT_{2B}R), which has been associated with cardiac valvulopathy, raises serious safety concerns, underscoring the need for subtype-selective psychedelics. To address this, we determined the cryo-EM structure of 5-HT_{2A}R and performed a comparative structural analysis of the orthosteric binding pockets (OBPs) of 5-HT_{2A}R and 5-HT_{2B}R. Guided by key residue differences, we developed a trigonal pharmacophore model to inform the design of 5-HT_{2A}R-selective agonists that avoid 5-HT_{2B}R activation. Using this model, we designed and synthesized two novel compound series that selectively activate 5-HT_{2A}R while antagonizing 5-HT_{2B}R. Cryo-EM structures of receptor-ligand complexes confirmed the molecular basis of subtype selectivity. These subtype-selective 5-HT_{2A} agonists also exhibited antidepressant-like efficacy in animal models. These findings provide a structural blueprint for the rational development of safer, subtype-selective psychedelic analogs with therapeutic potential.



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sciforum-166697: Selective activation of the kappa-opioid receptor by diphenethylamines, HS665 and HS666, for an effective and safer pain treatment

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Effective chronic pain treatment remains an unmet medical need as the currently available analgesics acting at the mu-opioid receptor (MOR) are either ineffective or have multiple and severe adverse effects. Among alternative treatment strategies, the kappa-opioid receptor (KOR), an important GPCR, is viewed as a promising target for development of pain therapeutics without the deleterious adverse effects of the MOR. Our group reported on diphenethylamines, as a new class of selective KOR ligands, with HS665 and HS666, emerging as G protein-biased KOR agonists. In this study, we report on the antinociceptive effects of HS665 and HS666 in models of inflammatory pain and their liabilities on locomotor activity and anxiety-like behavior in mice after s.c. administration. Additionally, in vitro functional KOR activity of HS665 and HS666 in mouse striatum, and pharmacokinetic properties were investigated. Both, KOR agonists effectively and potently inhibited pain behavior in the formalin test, and significantly reversed thermal hyperalgesia (the Hargreaves test) in Complete Freund's Adjuvant (CFA)-induced inflammatory pain in mice. Antinociceptive effects was reversed by the selective KOR antagonist, nor-binaltorphimine, demonstrating a KOR-dependent mechanism of action. In the rotarod and open-field tests, no significant sedation or altered locomotor activity were measured at therapeutic antinociceptive doses. In the elevated-plus maze test, the KOR agonists did not induce anxiety-like behavior. In the [³⁵S]GTPγS binding assay, HS665 and HS666 stimulated G protein signaling in striatum from wild-type mice, whereas no stimulation was measured in KOR-knock-out mice. Additionally, diphenethylamines show high stability in the mouse plasma and are brain penetrant. In summary, we show that selective KOR agonists HS665 and HS666 are effective antinociceptives in experimental inflammatory pain and displays a favorable benefit/side effect ratio regarding CNS-mediated KOR side effects. Targeting the KOR represents a promising strategy for an improved and safer treatment of pain conditions.



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Session 6. New Proximity-Based Drug Modalities

sciforum-169473: Design and Synthesis of TDP-43-Directed Latrepirdine (Dimebon™)-Based Proteolysis-Targeting Chimeras (PROTACs)

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Latrepirdine (also known as dimebolin and/or Dimebon™) has been shown to inhibit the pathological TAR DNA binding protein of 43 kDa (TDP-43) aggregates in cellular models.[1] TDP-43 plays a key pathogenic role in several neurodegenerative diseases, including amyotrophic lateral sclerosis, frontotemporal dementia, and also Alzheimer's disease (AD), where it aggravates the pathology produced by other aggregative proteins, namely β -amyloid peptide and tau protein. Thus, TDP-43 is a very relevant therapeutic target for the treatment of these diseases. Given its central role in neurodegeneration, targeted protein degradation of TDP-43 using a PROTAC-based approach represents an attractive therapeutic strategy.

Here, we present our recent work on the design, synthesis and biological investigation of novel TDP-43 degraders. The TDP-43-directed latrepirdine-based PROTACs were built by tethering the free NH group of the 1,2,3,4-tetrahydro- γ -carboline moiety of the TDP-43 ligand to lenalidomide, a cereblon E3 ligase ligand, *via* either a short methylcarbonyl linker or polyethylene glycol (PEG) linkers of varying lengths. Results of degradation activity in neuroblastoma SH-SY5Y cells demonstrated that the PROTAC bearing the shortest linker exhibited the most pronounced degradation activity, inducing a dose-dependent reduction of TDP-43 protein levels, effectively reducing TDP-43 levels at 10 and 100 μ M concentrations, as determined by Western blot analysis.

Reference

1. Yamashita, M. *et al.*, *FEBS Lett.*, **2009**, *583*, 2419–2424.



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sciforum-165429: Hijacking Phosphatases for Target Protein Dephosphorylation with Phosphorylation Targeting Chimeras (PhosTACs)

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Protein phosphorylation is the most fundamental and important mechanism for the regulation of protein function and signal transduction, and is involved in nearly all physiological and pathological processes. We recently developed a heterobifunctional approach [phosphorylation targeting chimeras (PhosTACs)] to achieve the targeted protein dephosphorylation (TPDephos), PhosTAC induces dephosphorylation of the target protein by recruiting both the target protein and phosphatase into close proximity.

First, we used small molecule-based PhosTACs to recruit tau to PP2A, a native tau phosphatase. PhosTACs induced the formation of a stable ternary complex, leading to rapid, efficient, and sustained tau dephosphorylation, which also correlated with the enhanced downregulation of tau protein. Mass spectrometry data validated that PhosTACs downregulated multiple phosphorylation sites of tau. We believe that PhosTAC possesses several advantages over current strategies to modulate tau phosphorylation and represents a new avenue for disease-modifying therapies for tauopathies.

Then, we envisioned combining the inhibitory effects of receptor tyrosine kinase inhibitors (RTKIs) and the active dephosphorylation by phosphatases to achieve dual inhibition of kinases. We report an example of tyrosine phosphatase-based TPDephos and the effective epidermal growth factor receptor (EGFR) tyrosine dephosphorylation. We also used phosphoproteomic approaches to study the signaling transductions affected by PhosTAC-related molecules at the proteome-wide level. This work demonstrated the differential signaling pathways inhibited by PhosTAC compared with the TKI, gefitinib. Moreover, a covalent PhosTAC selective for mutated EGFR was developed and showed its inhibitory potential for dysregulated EGFR. Last, EGFR PhosTACs, consistent with EGFR dephosphorylation profiles, induced apoptosis and inhibited cancer cell viability during prolonged PhosTAC treatment. PhosTACs showcased their potential of modulating RTKs activity, expanding the scope of bifunctional molecule utility.



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sciforum-165750: Targeting the “undrugged” SMAD4 protein with mutation-directed molecular glues

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Cancer genome sequencing has revealed that loss-of-function mutations in tumor suppressor genes are among the most common drivers of human malignancies, yet these targets remain largely undruggable because such mutations often disrupt large protein–protein interaction (PPI) interfaces rather than creating enzymatic liabilities. An emerging opportunity lies in exploiting mutation-altered PPIs using proximity-based drug modalities, particularly molecular glues that stabilize or re-engineer weakened interactions. Using the TGF- β pathway tumor suppressor SMAD4 as a model, we developed a systematic, unbiased chemical screening platform to identify small molecules capable of restoring mutation-attenuated PPIs. In our initial study, we discovered a first-in-class SMAD4-R361H-directed molecular glue that non-covalently stabilizes the SMAD4/SMAD3 complex, reactivating tumor-suppressive transcriptional signaling and establishing proof-of-principle that hypomorphic tumor suppressor PPIs can be functionally rescued by small molecules. Building on this framework, we recently identified a distinct class of mutation-directed covalent molecular glues targeting SMAD4-R361C, a cancer-acquired neo-cysteine located at the PPI interface. Through chemoproteomic profiling, biochemical validation, and cellular assays, we demonstrate that an amino-benzothiazole-based warhead selectively engages this neo-cysteine to stabilize the SMAD4/SMAD3 interaction and restore downstream transcriptional activity. Together, these studies illustrate how mutation-encoded structural and chemical features can be leveraged as precise molecular handles for proximity pharmacology, defining a generalizable strategy to expand molecular glue discovery toward undruggable tumor suppressors and the broader neo-cysteinome across cancer and genetic disease.



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sciforum-165883: An enzalutamide based D2B library approach provides a discovery tool for novel Androgen receptor degrader

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The androgen receptor (AR) remains a central therapeutic target in prostate cancer, yet resistance to current AR pathway inhibitors such as enzalutamide frequently emerges. Targeted degradation of AR represents a promising strategy to overcome these limitations. Here, we describe a Direct-to-Biology (D2B) small-molecule screening approach to identify novel AR degraders using an enzalutamide-based library.

An enzalutamide warhead was chemically coupled to an in-house curated small-molecule library to explore degrader-like chemical space beyond classical PROTAC architectures. The resulting library was screened in KBM7 cells engineered to overexpress AR fused to the HiBiT tag, enabling a sensitive and quantitative luminescence-based readout of AR protein levels. The clinically advanced AR degrader ARV-110 was included as a positive control and benchmark for degradation efficacy.

From this screen, multiple hit compounds were identified that induced robust and reproducible AR degradation in the AR-HiBiT assay. Selected hits were further validated in an orthogonal KBM7 AR-GFP reporter cell line, where flow cytometry confirmed a significant reduction in AR-GFP protein levels. Importantly, AR degradation by these compounds was also observed in LNCaP prostate cancer cells, demonstrating activity in a disease-relevant cellular context expressing endogenous AR.

These findings highlight the utility of enzalutamide-derived D2B libraries to discover non-canonical AR degraders and expand the chemical modalities capable of inducing AR degradation. Future work will focus on elucidating the mechanisms of action, optimizing potency and selectivity, and assessing the potential of these compounds to overcome resistance to current AR-targeted therapies.



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sciforum-175792: Biocatalytic- and Chemoproteomic-Guided Discovery of a PHGDH Inhibitor from Chemoenzymatic-Promoted DNA-Encoded Libraries Selection Platform

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DNA-encoded libraries (DELs) have emerged as an effective and efficient selection strategy for lead compound discovery in academia and industry over the past few decades. Despite recent advancements in this field, DEL remains limited by sensitive DNA-based constructs, particularly with low selection success rates resulting from the random selection of targets. Here, we describe a chemoenzymatic on-DNA reaction for DEL syntheses and develop a chemoproteomic-guided DEL selection platform. This platform, termed FF tags-biocatDEL, integrates DEL technology, chemoenzymatic synthesis, and fully functionalized (FF) chemical tags to match DELs with selection targets, even with limited information about ligandable hotspots. Using two diazirinebased FF indole probes, we comprehensively surveyed binding partners in cells and identified phosphoglycerate dehydrogenase (PHGDH) as a potential target for DEL selection. DEL01 and DEL02 were designed, synthesized, and selected against PHGDH, leading to the identification of a novel enzyme-active compound with an IC₅₀ value of 2.5 μ M. Our strategy, utilizing FF tags-biocatDEL, establishes a generalizable workflow for rapid target hunting and ligand discovery. Compared with the conventional approach of random protein selection, chemoproteomic-guided DEL selection significantly improved the efficiency of ligand discovery, particularly for proteins containing ligandable hotspots. This methodology can be taken as an efficient complementary solution in DEL-based targeted drug discovery strategies.



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sciforum-172134: Discovery of Novel E3 Ligase Ligands to Unlock the Power of Targeted Protein Degradation

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Targeted protein degradation (TPD) drugs, including proteolysis-targeting chimeras (PROTACs) and molecular glue degraders (MGDs), are emerging as a class of transformative drug modalities. These drugs typically function by inducing proximity between a protein of interest (POI) and an E3 ligase, leading to POI ubiquitination and subsequent degradation via the proteasome. However, only a limited number of E3 ligases (mainly CRBN and VHL) have been used as TPD effectors, which limits the full potential of TPD drugs. To unlock the power of over 600 E3 ligases and other potential effectors, we have developed a platform to identify "PROTACable" sites on E3 ligases using Site-specific Ligand Incorporation-induced Proximity (SLIP). The platform uses a genetic code expansion (GCE) system to precisely incorporate a strain-promoted (Cu-free) "clickable" unnatural amino acid (UAA) into an E3 ligase. This enables the ligase to click with a POI ligand, generating a PROTAC on the E3 surface that drives POI degradation. Ligand-modified effectors drive degradation of the targeted protein specifically at privileged actionable sites, establishing their PROTACability. Using SLIP, we identified and validated several promising PROTACable effectors and sites across dozens of ligases, which informs our site-specific E3 ligase ligand discovery using DNA-encoded library. This work will help guide E3 ligand discovery and fully enable the potential of TPD drug discovery.



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sciforum-165108: Extracellular HSP90-Facilitated Degradation of Extracellular and Membrane Proteins by Bifunctional Small Molecules

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Lysosome-targeting chimeras (LYTACs) have emerged as a promising therapeutic approach for degrading extracellular and membrane proteins by exploiting the endogenous lysosomal degradation pathway. LYTACs expand the scope of targeted protein degradation beyond the intracellular proteasome system, enabling the elimination of secreted and surface-exposed proteins that are not amenable to traditional small-molecule inhibitors or proteasome-based degraders such as PROTACs. However, the repertoire of available receptors for LYTACs remains limited. Herein, we reported a novel strategy utilizing extracellular heat shock protein 90 (eHSP90) to facilitate lysosomal degradation of target proteins through bifunctional small molecules, termed extracellular Heat Shock Protein 90 Targeting Chimeras (eHSPTACs). By connecting an HSP90 ligand to a target protein ligand, eHSPTACs effectively induced the internalization and subsequent lysosomal degradation of extracellular Alexa Fluor 488 (AF488)-labeled α -DNP antibody and membrane programmed cell death-ligand 1 (PD-L1). Notably, the membrane PD-L1 eHSPTAC, **dPDL1-4** selectively degraded membrane PD-L1 in tumor cells over normal cells, leveraging the elevated expression of eHSP90 in cancer cells. Moreover, **dPDL1-4** demonstrated robust in vivo degradation of membrane PD-L1 and significant tumor growth suppression in B16F10 syngeneic mouse model. Overall, eHSPTACs offer a general platform for tumor-selective degradation of extracellular and membrane proteins, providing a new avenue for therapeutic intervention.



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sciforum-178720: Molecular targets of CNEURO-201 in Alzheimer's disease: data from biophysical, cellular and animal studies

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Neurodegenerative diseases, including Alzheimer's disease (AD), are characterized by pathological protein aggregation – a key hallmark of proteinopathies. Among promising therapeutic agents, the class of naphthalene derivatives CNEURO-201 stands out. The goal of our study was to characterize the pharmacological properties and elucidate the molecular mechanisms of action of these compounds. Amylovis-1 demonstrated the lowest cytotoxicity (IC₅₀ = 9,1 mM) compared to Amylovis-2 (3,1 mM) and Amylovis-3 (1,4 mM). In the cellular model of proteinopathy, Amylovis-1 showed the highest activity in suppressing protein aggregation. The results of molecular modeling and isothermal titration calorimetry showed that Amylovis-1 binds stably to the Aβ₁₋₄₂ peptide (K_D = 0,68 μM). The key interaction sites are located in regions 17–22 and 35–40 of the peptide and include residues Phe19 and Phe20. The binding is entropically driven. Compounds of the Amylovis class exhibited negligible inhibition of AChE and BuChE (≤ 4.5 % at 20 μM) and showed low antiradical activity in the ABTS assay. Chronic administration of CNEURO-201 to 5xFAD model mice of AD failed to reverse the phenotypic behavioral changes, however significantly decreased amyloid burden in frontal cortex and hippocampus. The comprehensive analysis confirms that Amylovis-1 is a promising neuroprotective agent with a targeted mechanism of action aimed at suppressing Aβ aggregation. The favorable cytotoxicity profile and the ability to modulate protein aggregation in cellular models justify further development of the compound as a potential therapeutic agent for Alzheimer's disease and related proteinopathies. The research is supported by the grant agreement No. 075-15-2025-289.



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sciforum-172307: Novel Nanodrug Based on Proximity Effect

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Building upon the induced proximity nanotechnology we developed, this research systematically explores its transformative potential in regulating inter-organelle interactions and manipulating biological processes at the molecular level. By integrating theoretical simulations with precisely engineered nanomaterials, we have established a robust platform for controlling protein spatial conformations, protein complex dynamics, and organelle communication within defined spatial parameters. The technology enables real-time manipulation of biological interactions through tunable nano-inducers that create transient molecular bridges between target proteins and organelles, allowing us to decipher previously inaccessible biological mechanisms. The technology's modular design allows adaptation to various biological systems, with current data showing 89% specificity in targeting intended molecular pairs. Our experimental validation demonstrates three groundbreaking applications: First, in protein misfolding diseases, we achieved precise correction of pathological protein aggregates by orchestrating chaperone recruitment through nanoparticle-mediated proximity. Second, in cancer models, we successfully enhanced immunotherapeutic efficacy by forcing interactions between tumor antigens and antigen-presenting machinery using engineered nano-inducers. Third, our mitochondrial-ER coupling experiments revealed new pathways in cellular metabolism regulation, showing 3.2-fold increase in calcium signaling efficiency compared to conventional methods. This approach not only provides unprecedented spatiotemporal control over cellular processes but also establishes a new paradigm for therapeutic intervention. Future directions will focus on developing stimulus-responsive nano-inducers for precise in vivo applications and expanding the technology to neurodegenerative disease models. Through continued refinement, this platform promises to unlock new dimensions in precision medicine and fundamental biological research.



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sciforum-176211: Proximity-Based Small Molecules for Induced Dephosphorylation

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In recent years, bifunctional molecules based on induced proximity have revolutionized drug discovery beyond traditional strategies. By establishing specific spatial proximity between biological effectors and proteins of interest (POIs), these chimeras enable precise, site-specific post-translational modifications, especially phosphorylation. Two representative classes have been developed: Phosphorylation-Inducing Chimeric Small molecules (PHICS) and Phosphatase Recruiting Chimeras (PHORC), which recruit kinases or phosphatases to modulate phosphorylation status, respectively. Notably, PHORC shows unique and promising value in targeted dephosphorylation, which is particularly critical for human diseases driven by pathological hyperphosphorylation, such as cancer and neurodegenerative disorders. In contrast to conventional kinase inhibitors that only block phosphorylation, PHORC actively mediate site-specific dephosphorylation by recruiting endogenous phosphatases to target proteins. This mechanism achieves high substrate selectivity without globally activating phosphatase activities, thereby greatly reducing off-target effects and toxicities. Compared with PHICS, PHORC provides a complementary and powerful strategy to reverse aberrant phosphorylation signaling, restore cellular homeostasis, and overcome drug resistance commonly encountered in long-term kinase inhibitor therapy. Moreover, the modular design of PHORC facilitates flexible optimization of target binding, linker properties, and phosphatase recruitment efficiency, further enhancing its potential as a versatile and tunable platform for targeted dephosphorylation in both basic research and therapeutic development. In this presentation, I will introduce a PP5-based PHORC molecule to achieve potent dephosphorylation effect.



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sciforum-175613: PSMA-Mediated Target Protein Degradation Enables Selective and Effective Therapy for Prostate Cancer

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The clinical translation of potent protein degraders is often hindered by suboptimal drug-like properties and on-target toxicity in healthy tissues. To overcome these challenges, we developed a novel strategy that redirects the activity of highly potent degraders selectively to prostate cancer cells by conjugating them with a ligand for prostate-specific membrane antigen (PSMA), a surface marker abundantly expressed in prostate cancers. Using our non-tumor selective AKT-targeting PROTAC MS21, we demonstrate that the resulting conjugates are selectively internalized through PSMA-mediated endocytosis, followed by tumor-specific linker cleavage to release active MS21. This two-step targeting process-receptor-selective delivery followed by conditional activation, resulted in potent AKT degradation and robust antiproliferative effects in PSMA-positive cells. Our lead conjugate, CQ-170, exhibited superior *in vivo* antitumor efficacy, alongside a significantly enhanced tumor-targeting selectivity compared to the parent MS21. Moreover, to demonstrate the platform's broad applicability, we successfully retargeted the toxic GSPT1 molecular glue CC-885, achieving potent on-target activity in tumor while drastically reducing its toxicity in normal cells. Collectively, this work provides a robust and modular targeting strategy that decouples potent degrader efficacy from systemic toxicity. By conferring precise tumor tissue selectivity, this approach unlocks the full potential of diverse degrader modalities for prostate cancer precision oncology.



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sciforum-167611: RIMTAC: A Novel Degradation Design Platform by Indirect VHL-Recruitment via RIPK1

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Proteolysis-targeting chimeras (PROTACs) offer a powerful therapeutic strategy for targeted protein degradation, yet their development is constrained by a limited repertoire of E3 ligase ligands. Conventional VHL-based PROTACs, which employ direct VHL inhibitors, carry inherent risks of impairing VHL's tumor-suppressive function and often exhibit poor oral bioavailability. To address these limitations and expand the E3 ligase toolbox, we developed a novel strategy termed RIPK1-Mediated Targeting Chimeras (RIMTAC). RIMTAC bypasses direct VHL inhibition by utilizing a RIPK1 inhibitor to hijack the endogenous RIPK1-VHL complex, thereby indirectly recruiting the VHL E3 ligase machinery for targeted degradation. As a proof of concept, we designed and synthesized RIMTACs targeting BRD4, AKT, and JAK1, respectively. These RIMTACs induced potent, concentration- and time-dependent degradation of their respective targets in HEK-293T cells. Degradation was mechanistically confirmed to depend on the ubiquitin-proteasome system and required the formation of a quaternary complex involving VHL, RIPK1, the target protein, and the RIMTAC modality. Collectively, the RIMTAC platform provides a versatile and effective strategy to indirectly recruit the VHL while potentially circumventing key drawbacks associated with traditional VHL inhibitor-based PROTACs, thereby provides a valuable addition to the targeted protein degradation (TPD) arsenal. Moreover, RIMTAC is suitable for degrading inflammation-associated targets and could act synergistically with RIPK1 inhibition to enhance anti-inflammatory efficacy.



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sciforum-178186: Small-Molecule Degraders for Oncogenic KRAS^{G12C} and Pan-KRAS Mutations

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Kirsten rat sarcoma viral oncogene homolog (KRAS), one of the most frequently mutated oncogenes in cancer, has long posed a formidable therapeutic challenge due to the difficulty of directly inhibiting its activity. A major breakthrough emerged with the development of covalent, allele-specific inhibitors targeting KRAS^{G12C}, such as sotorasib. However, the clinical utility of these inhibitors is frequently limited by the rapid development of acquired resistance. Targeted protein degradation (TPD) has emerged as an effective approach with the potential to overcome drug resistance, but it has been mostly restricted to large-size proteolysis-targeting chimeras (PROTACs). In this study, we present the first small-molecule KRAS^{G12C} degrader, **DJX-A-KM**, designed by integrating a simple acrylamide warhead into the hydrophilic moiety of the MRTX849 scaffold. **DJX-A-KM** induces rapid, robust, and sustained degradation of KRAS^{G12C} in both cellular and animal models (DC₅₀: 2 nM; D_{max}: 98%; 60h durability), demonstrating superior pharmaceutical properties to PROTACs. Mechanistic investigations revealed that degradation is mediated by the ubiquitin-proteasome system, facilitated by covalent engagement with a new E3 ligase, FBXO28, at cysteine 98 through the acrylamide warhead. Antiproliferation assays demonstrated its potent inhibitory effects across multiple KRAS^{G12C}-mutant cancer models, with *in vivo* studies confirming significant tumor growth suppression mediated by targeted KRAS^{G12C} degradation. Notably, this chemical strategy extends beyond KRAS^{G12C}, offering a blueprint for developing pan-KRAS degraders against a broader spectrum of KRAS mutations. To our knowledge, this study reports the first small-molecule degrader that recruits FBXO28 as an E3 ligase, employing a novel dual covalent strategy to achieve the highest targeted degradation of KRAS^{G12C} thus far. Additionally, it represents the first small-molecule pan-KRAS degrader and provides a feasible approach for exploring new E3 ligases in targeted protein degradation applications.



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sciforum-163302: Surface Chemistry for the Generation of Luminescent DNA-Encapsulated Silver Nanodots

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Introduction

Luminescent silver nanodots (AgNDs) are highly stable silver clusters encapsulated within molecular scaffolds, exhibiting spectrally pure emissions from the blue to near-infrared regions. While AgND generation in solution has been extensively studied, the formation and behavior of AgNDs on surfaces remain poorly understood. Given that nanodot stability relies strongly on coordinated covalent interactions between the silver cluster core and surrounding ligands, surface chemistry is expected to play a critical role in determining AgND generation, stabilization, and optical properties.

Methods

We investigated the generation of AgNDs on surfaces functionalized with printed single-stranded DNA (ssDNA). Different pathways for AgND formation were examined, including direct chemical reduction, photoactivation, and silver cluster transfer. The effects of surface confinement, ssDNA mobility, and cation interactions on nanodot generation and photophysical properties were systematically analyzed.

Results

Our results reveal that AgND generation on surfaces fundamentally differs from that in solution. Adsorbed ssDNA does not efficiently support nanodot formation via reduction or photoactivation. Instead, AgNDs are rapidly generated through silver cluster transfer, occurring significantly faster than solution-based synthesis. Notably, near-infrared-emitting AgNDs dominate on surfaces, in contrast to the red emitters commonly formed in solution, likely due to preferential surface stabilization. Surface-induced kinetic trapping of ssDNA restricts structural reorganization, limiting the formation of alternative emissive species. By tuning the conformational freedom of surface-bound ssDNA, diverse AgND emitters can be selectively generated. Additionally, loosely protected AgNDs exhibit sensitivity to cations, which modulate nanodot rigidity and photophysical behavior.

Conclusions

These findings highlight the critical role of surface chemistry in controlling AgND generation and emission, offering new strategies for spectral tuning and surface-based sensing applications.



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sciforum-167486: Synthesis of PTP1B-Targeting PROTACs and Their Anti-Type 2 Diabetes Activity

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Introduction

Protein tyrosine phosphatase 1B (PTP1B) is a well-established negative regulator of insulin signaling and a key therapeutic target for type 2 diabetes mellitus and insulin resistance. However, the development of conventional small-molecule PTP1B inhibitors has been hindered by poor selectivity and limited cellular permeability, largely due to the highly conserved and positively charged nature of its catalytic site. Proteolysis-targeting chimera (PROTAC) technology, which induces selective degradation of target proteins, offers a promising strategy to overcome these limitations and address traditionally “undruggable” targets such as PTP1B.

Methods

A series of PTP1B-targeting PROTACs were rationally designed and synthesized. A highly potent and selective PTP1B inhibitor (compound 5E, $IC_{50} = 82$ nM, >20-fold selectivity over TCPTP), as well as the natural products oleanolic acid and ursolic acid, were employed as PTP1B ligands. Pomalidomide was used as a cereblon (CRBN) E3 ligase recruiter. Various short- to medium-length linkers containing linear oxygenated chains or cyclic aliphatic amines (piperazine or piperidine) were introduced, and the components were connected via stable C–N or C–O bonds.

Results

Western blot analysis demonstrated that PROTACs derived from inhibitor 5E induced robust and selective degradation of PTP1B in vitro. Among them, compound GY-66 showed the most potent activity, with a DC_{50} value of 0.6 nM and a clear time-dependent degradation profile. In db/db diabetic mice, 21-day treatment with GY-66 significantly reduced postprandial blood glucose levels to near-normal values. Moreover, in oral glucose tolerance tests, GY-66 exhibited a glucose-lowering effect superior to that of the positive control drug metformin.

Conclusion

This study represents the first application of PROTAC-based protein degraders in anti-diabetic research and provides a novel therapeutic strategy for targeting PTP1B. The results highlight the potential of PTP1B degraders as next-generation glucose-lowering agents with high efficacy and durable pharmacological effects.



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sciforum-177420: Targeted Degradation of TDP-43: A PROTAC-Based Therapeutic Approach for ALS and Alzheimer's Disease

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The pathological aggregation of TAR DNA-binding protein 43 (TDP-43) represents a key hallmark of amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD) and, increasingly, Alzheimer's disease (AD).¹ Conventional small molecules have failed to modulate this intrinsically disordered protein, rendering TDP-43 an “undruggable” target.²

Here, we report a novel targeted protein degradation strategy combining different design principles to induce selective elimination of TDP-43. A recombinant TDP-43 (1–260) construct enabled ligand discovery through anti-aggregation screening. The most promising binders were incorporated into rationally designed PROTACs recruiting different E3 ligases and exploring linker composition and length to optimize degradation efficiency, stability, and CNS permeability.

Several chimeras exhibited favourable PAMPA-BBB permeability and induced dose-dependent degradation of TDP-43 in SH-SY5Y neuronal cells, as confirmed by western blot analysis. Notably, multiple compounds achieved >70% target depletion at 1–50 μ M without cytotoxicity.

These results describe the **first generation of brain-permeable TDP-43 degraders**, providing a promising starting point for disease-modifying therapeutic strategies targeting TDP-43 proteinopathies in ALS, FTLD and AD.

We acknowledge the funding from grants PID2023-147004OB-I00 to D.M.T, funded by MICIU/AEI/10.13039/501100011033 and by “European Union NextGenerationEU/PRTR”, and J.S. thank the Spanish MICIU for PhD Grants (FPI program).

References

1. Nathan K.N. et al. ACS Chem. Neurosci. 2025, 16, 2450–2462.
2. Tseng Y.L. et al. J. Biomed. Sci. 2023, 30, 27.



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sciforum-165186: Targeting E3 Pseudoligases via Proximity-Based Protein Abundance Control: TRIM15 as a Case Study

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Introduction

Targeting E3 ubiquitin ligases represents a frontier in drug discovery, yet a significant subset functions as “pseudoligases” rather than standalone enzymes, rendering them challenging targets for developing traditional occupancy-based modulators. TRIM15, an underexplored but essential regulator implicated in antiviral defense and inflammatory responses, exemplifies this pharmacological hurdle. While its intrinsic catalytic activity remains controversial given reported enzymatic activities in other pathological contexts, its function as a scaffolding protein establishes it as a key facilitator in innate immunity. Here, we propose that chemically modulating proximity to directly tune protein abundance offers a viable targeted protein modulation approach for such targets.

Methods

We initiated a large-scale screen targeting the human TRIM15, which yielded several high-affinity binders that engage non-overlapping pockets. Following subsequent optimization, we applied an orthogonal chemical genetic strategy by designing proteolysis-targeting chimeras to induce proximity with CRBN for degradation and developing chemical stabilizers to block the proximity between TRIM15 and its endogenous E3 ligase. The biological effects were evaluated using immunoblotting, co-immunoprecipitation, antiviral and anti-inflammatory assays in biologically relevant cell models.

Results

We developed the first selective degraders and mechanistically novel stabilizers for TRIM15 to modulate immune signaling. The degrader induced rapid, proteasome-dependent clearance of TRIM15 and significantly suppressed Poly(I:C)-induced inflammatory cytokine secretion. Conversely, the stabilizer competitively blocked the recruitment of a specific endogenous E3 ligase, preventing TRIM15 turnover, which significantly enhanced innate immune responses and exhibited broad-spectrum efficacy against DNA and RNA viruses.

Conclusions

This study provides the first pharmacological toolkit for TRIM15 and validates it as a druggable target. By employing targeted protein degradation and stabilization, we demonstrated that modulating protein abundance is a rational strategy for targeting proteins with debated enzymatic functions. This work establishes a generalizable framework for drugging the broader landscape of pseudoenzymes and scaffold proteins via proximity-driven, context-dependent chemical control.



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sciforum-167771: The converging mechanism of a molecular glue degrader and cancer gain-of-function mutations

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Targeted protein degradation, particularly via molecular glue degraders, has revolutionized drug discovery with its simplicity and favorable pharmacological properties. However, only a limited number of molecular glues have been identified and only a few E3 ligases found glue-able to date. Expanding this repertoire is crucial for advancing our understanding of molecular glue mechanisms, E3 ligase interactions, and their therapeutic applications.

For the first time, our study defines the target and mechanism of a new molecular glue degrader UM171 that utilizes a dimeric CULLIN3 E3 ligase (KBTBD4) to degrade a transcription corepressor CoREST complex. This research unveils an asymmetric E3 architecture that not only provides fundamental insights into E3 structure and function but also sets the groundwork for targeting a previously inaccessible, extensive class of ligases for protein degradation.

Remarkably, the recurring mutations on KBTBD4 found in medulloblastoma, confers gain-of function to KBTBD4 to induce degradation of the same substrate CoREST complex. The cancer mutations resemble chemical glue UM171 functionally, structurally, and mechanistically, elucidating the converging mechanisms between molecular glue degraders and cancer gain-of-function mutations, portraying cancer mutations as "genetic glues." This resemblance shed lights on novel molecular glue design by using massively parallel genetic methods, potentially transforming therapeutic strategies in diseases.



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Session 7. Biocatalysis for Natural Product and Drug Synthesis

sciforum-180727: Merging Natural and Unnatural Reactivity of Reductive Aminases for Stereoselective Thioamination Cascade Reactions

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Carbon–heteroatom bond formations are very important reactions in organic synthesis. While chiral C–N and C–S bonds are pivotal scaffolds in pharmaceuticals and bioactive molecules. The construction of C–N bonds via reductive amination is a cornerstone reaction in pharmaceuticals, mirroring the critical prevalence of C–S bonds in synthetic drugs and living organisms. However, prevailing synthetic methods rely heavily on precious metal catalysts often suffer from environmental concerns, high cost and lack general stereoselectivity, especially for constructing congested centers. Herein, we present a biocatalytic solution via the merged natural and unnatural reactivity of reductive aminases for stereoselective thioamination cascades. This one-pot biocatalytic process converts readily available α,β -unsaturated carbonyls, thiols, and amines into valuable chiral thioamines with high yields and excellent diastereo- and enantioselectivity over up to three stereocenters. This strategy was further extended by coupling it with chiral resolution and integrating alcohol dehydrogenases to establish a redox-neutral process, thereby enhancing its utility and demonstrating broad applicability. Key mechanistic and structural studies elucidate the sequence of an amine-activated stereocontrolled thio-Michael addition followed by asymmetric reduction amination, enabled by a tailored active site. This merged reactivity paradigm highlights a powerful, sustainable platform for the stereodivergent synthesis of valuable targets containing multiple chiral carbon-heteroatom bonds.



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sciforum-178024: Concise construction of β -branched aromatic D-amino acids via transaminase-catalyzed dynamic kinetic resolution

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D-amino acids (DAAs), the enantiomers of naturally occurring L-amino acids (LAAs), have garnered substantial attention in medicinal chemistry, materials science, and biotechnology owing to their unique biological functions and diverse applications. Unlike their L-enantiomeric counterparts, DAAs exhibit exceptional stability against enzymatic degradation, specific receptor-binding affinity, and distinct conformational characteristics, which make them indispensable building blocks for the development of novel bioactive molecules, functional biomaterials, and biotechnological tools. Recent years have witnessed remarkable advances in the biocatalytic synthesis of non-canonical amino acids (ncAAs), with enzymes including transaminases, dehydrogenases, and ammonia lyases being widely employed. The molecular frameworks of β -branched aromatic D-amino acids are critical for the pharmaceutical efficacy of bioactive compounds, as they modulate spatial conformation, receptor-binding modes, and pharmacokinetic properties. However, the limited availability of efficient synthetic methods for β -branched D-amino acids has severely impeded progress in structure-activity relationship (SAR) studies. Herein, we report the asymmetric synthesis of β -branched aromatic D-amino acid analogues catalyzed by PLP-dependent transaminase BsDAAT (from *Bacillus* sp. strain YM-1), an efficient transamination system that operates via dynamic kinetic resolution (DKR). Through molecular docking analysis and rational enzyme engineering, we successfully synthesized a series of β -substituted aromatic D-amino acids with high yields (up to 99%), diastereomeric ratios (dr > 20:1), and enantiomeric excess (ee) values (up to 99%). Furthermore, these β -branched aromatic D-amino acids were successfully incorporated into the structural modification of the antineoplastic agent lanreotide.



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sciforum-181668: Convergent Total Synthesis and Structural Revision of (-)-Papililone A via Pd-Catalyzed Alkenylation/Cyclization Cascade

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Papililone A, a structurally complex polycyclic diterpenoid isolated from *Papilio* species, exhibits potent anti-inflammatory activity and features an unprecedented fused-bridged 5/5/5/6 tetracyclic core with six contiguous stereocenters, including two adjacent all-carbon quaternary bridgehead centers. Its intricate architecture presents significant challenges for chemical synthesis and structural assignment. Herein, we report the first total synthesis of both ($\pm$)-papililone A and enantiomerically pure (-)-papililone A, leading to a revision of the originally proposed structure. Initial synthetic approaches, relying on nitrile polar-radical cyclization to form a 5/4-fused cyclobutanone and zirconium-mediated vinyl iodide synthesis, encountered inefficiencies in fragment coupling and undesired stereochemical outcomes in a key rearrangement. A redesigned strategy employed a 3-bromofuran building block to enable efficient assembly of a critical intermediate. Subsequent oxidation and stereoselective rearrangement delivered the 5/5-bicyclic core with high diastereocontrol. The synthesis culminated in a novel tandem alkenylation/6-endo-trig cyclization, enabling the construction of the fused-bridged 5/5/6 tricyclic scaffold and furnishing ($\pm$)-papililone A as a single diastereoisomer. Comparative NMR analysis, NOE experiments, and, most critically, X-ray crystallographic data of a synthetic sample unambiguously established the correct C17 stereochemistry, revising the originally proposed structure. The absolute configuration of natural (-)-papililone A was confirmed by CD spectroscopy and optical rotation measurements. This work not only provides access to papililone A and its enantiomer but also corrects its structural assignment, offering a foundation for further biological and synthetic studies.



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sciforum-167117: Biocatalytic Synthesis of Chiral Amines toward Novel Drug Discovery

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Chiral amine structures play a pivotal role in the field of organic active pharmaceutical ingredients (APIs). Although chemosynthetic methods have made great efforts to solve the asymmetric synthesis of such functional groups, there are still existing limitations such as poor efficiency, selectivity as well as environmental crisis. Enzymatic catalysis, on the other hand, represents a green and efficient strategy to access amine fragments of APIs due to its efficiency, selectivity, ease of manipulation and reproducibility, and has attracted considerable attention from both academia and industry.

Here, we present two examples of chiral amine synthesis. First, we report an imine reductase (IRED)-catalyzed dynamic kinetic resolution strategy for the synthesis of atropisomeric biaryl amines, especially for (hetero)aryls bearing bulky substitutions. The selected IRED (IR-09) catalyzes a variety of naphthalene- and quinoline-containing biaryl aldehydes, producing the axial chiral amine products in high yields (up to 99%) and high ee values (up to 99%). Secondly, the D- β -branched phenylalanine analogues were successfully prepared via the catalysis of a D-Phe transaminase BsDAAT. The two adjacent chiral centres were constructed by a DKR process under enzyme catalysis. The specific non-canonical amino acids were obtained with good efficiency (up to 95% yield) and enantioselectivity (up to >20:1 dr and 99% ee).

With the chiral amine building blocks in hand, various drug-like molecules were constructed and evaluated.



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sciforum-161732: Biosynthesis and chemoenzymatic synthesis of ADP-heptoses

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Adenosine-diphosphate-D-glycero- β -D-manno-heptose (ADP-D,D-heptose) and its C-6'' epimer, ADP-L-glycero- β -D-manno-heptose (ADP-L,D-heptose) are potent agonists that can activate innate immunity. They also serve as precursors of heptose containing antibiotics like septacidin and spicamycin. The biosynthetic mechanism of ADP-heptoses have been elucidated in several bacteria. It starts from D-sedoheptulose-7-phosphate (S7P), which is converted to D-glycero-D-manno-heptose-7-phosphate (H7P) by an isomerase (GmhA). A following kinase (HldA) adds a phosphate group to the anomeric carbon to generate D-glycero- β -D-manno-heptose-1,7-biphosphate (HBP), which is hydrolyzed by a phosphatase GmhB to remove the 7-phosphate and activated by a nucleotidyltransferase HldC to form ADP-D,D-heptose. And, ADP-D,D-heptose can be converted to ADP-L,D-heptose by an epimerase HldD. Notably, The NDP-heptose biosynthetic enzymes (HBEs) distribute in numerous organisms and take several different forms. Herein, we introduce the characterization of new form of HBEs from varied microorganisms. Based on this, we developed a simple chemoenzymatic synthesis route to prepare ADP-D,D-heptose and its C-6'' epimer, ADP-L,D-heptose. By recruiting the bifunctional kinase-nucleotidyltransferase HldE, we converted the chemical synthesized D,D-heptose to heptose-1-phosphate and then to ADP-D,D-heptose, which simplified both the chemical synthesis and the enzymatic catalysis processes. The enzymatic conversion achieved an efficiency as high as $48.7 \pm 1.1\%$. Moreover, HldE displayed a high substrate promiscuity and could catalyze the formation of ADP-L,D-heptose efficiently, further broadening the application of this chemoenzymatic synthesis method.



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sciforum-177910: Complementary Synthesis of Atropisomeric C–N Biaryl Amines through Imine Reductase-Mediated Dynamic Kinetic Resolution

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Introduction

Axially chiral amines represent a valuable subclass of chiral molecules characterized by restricted rotation around a single bond, leading to stable atropisomers. Among these, C–N axially chiral indole amine scaffolds are privileged structures in bioactive natural products, pharmaceuticals, and chiral ligands. Despite their biological significance, enzymatic strategies for constructing C–N axially chiral indole frameworks remain underexplored compared to their C–C counterparts. Herein, we report an efficient biocatalytic approach for the synthesis of both enantiomers of C–N axially chiral biaryl amines.

Methods

An unconventional imine reductase (IRED) platform was employed to achieve efficient dynamic kinetic resolution (DKR) via reductive amination, enabling access to complementary enantiomers (R/S) of C–N axially chiral biaryl amines.

Results

Through systematic screening of IREDs and their mutants, we successfully catalyzed a broad range of aromatic amines, constructing a series of axially chiral indole amine derivatives with excellent yields and enantioselectivities (up to >99% yield and >99% ee for both R and S configurations). Density functional theory (DFT) calculations and molecular dynamics (MD) simulations elucidated the stereoselective control mechanisms of PIR-85, IR-09, and its mutant IR-09-M228F in the DKR process. Furthermore, gram-scale reactions and product derivatization experiments demonstrated the practical utility and synthetic potential of this catalytic platform.

Conclusion

We have developed a novel biocatalytic strategy for the synthesis of complementary enantiomers of C–N axially chiral indole amines via IRED-catalyzed DKR. This method overcomes the limitations of traditional catalytic systems and accommodates a diverse range of amine substrates, including aliphatic, cyclic, and aromatic amines. The combination of experimental and computational insights provides a solid foundation for future applications in asymmetric synthesis and drug discovery.



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sciforum-167474: Mechanistic insights into the biosynthesis of Pseurotin A in *Aspergillus fumigatus*

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Bacteria and fungi produce a vast array of biologically active secondary metabolites, constituting an extensive molecular repository with substantial pharmaceutical and industrial potential. Pseurotin A is a secondary metabolite of *Aspergillus fumigatus* (*A. fumigatus*) and other fungi with broad biological activities, such as a competitive inhibitor of chitin synthase, an inhibitor of B-cell proliferation, and IgE production. In *A. fumigatus*, the biosynthesis of pseurotin A is dependent on at least seven genes in a supercluster, including a Polyketide-nonribosomal peptide synthase (PKS-NRPS), PsoA, and a bifunctional enzyme, PsoF. PsoA consists of a highly reducing polyketide synthase (HR-PKS) and a single nonribosomal peptide synthase (NRPS) module. PsoF is a bifunctional enzyme featuring two distinct catalytic centers, including a CMT and a FAD-containing monooxygenase (FMO) domain. However, little is known about the molecular mechanism of the PsoA and PsoF in the biosynthesis of pseurotin A. Here, we reported the cryo-EM structures of the HR-PKS module of PsoA from *A. fumigatus* in the apo state and in complex with the cofactors, revealing a conserved PKS architecture similar to that of mammalian fatty acid synthase. Interestingly, a flexible motif in the active site of the ketosynthase (KS) domain was identified to govern the production of target compounds by modulating the pocket size of the active site. We also found the direct interaction between PsoA and PsoF, and mapped their contact regions. Our findings provide novel insights into the biosynthesis of pseurotin A and the molecular mechanism of PKS-NRPS enzymes.



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sciforum-180553: Novel Oxidative Amidases for the Efficient Synthesis of Amides

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Amide bond formation is a cornerstone of pharmaceutical synthesis. However, traditional chemical methods often rely on carboxylic acids as substrates and require stoichiometric amounts of coupling reagents, which severely limits functional group tolerance and atom economy. Consequently, there is a pressing need for greener and more efficient approaches to amide bond construction. Here, we repurposed a conventional aldehyde dehydrogenase into an unprecedented oxidative amidase (OxiAm) by redesigning its catalytic mechanism. By substituting key catalytic residues, we transformed the original hydrophilic catalytic pocket into a more hydrophobic and spacious environment, enabling amines to intercept the thioester intermediate and yield amides as the predominant products. This biocatalyst facilitates the formation of amide bonds between diverse aldehydes and amines under mild conditions with excellent chemo-, regio-, and enantioselectivity. Remarkably, widely available alcohols can also serve as starting materials through a multi-step enzymatic cascade involving alcohol dehydrogenase, OxiAm, and nicotinamide oxidase, utilizing molecular oxygen as the terminal oxidant while requiring only a catalytic amount of cofactor. Furthermore, this biocatalytic strategy enabled the streamlining of synthetic routes for several drug molecules, achieving improved atom and step economy. Our findings highlight the potential of this "new-to-nature" OxiAm in advancing the synthesis of structurally diverse pharmaceuticals through efficient amide bond formation.



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sciforum-177620: Steric-Adaptive Biocatalysis: Imine Reductase-Mediated Dynamic Kinetic Resolution for Atroposelective Synthesis of Hindered Biaryl Amines

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As an efficient and environmentally benign strategy, enzymatic catalysis has emerged with high reactivity and selectivity for atropisomeric structures. Atropisomeric biaryl amines are of great importance in drug development and asymmetric catalysis. However, substrates with steric hindrance are often poorly accepted by enzymes, as the immense pockets required are not commonly found in wild-type enzymes. In this work, an imine reductase (IREN)-catalyzed dynamic kinetic resolution (DKR) strategy is introduced for the synthesis of atropisomeric biaryl amines, especially those with bulky substitutions on (hetero)aryls, including naphthalene- and quinoline-containing biaryl scaffolds. A broad range of atropisomeric biaryl amines are obtained in up to 99% yield and 99% ee, enabled by the steric adaptability of IR-09. The successful 1 mmol-scale reaction and subsequent derivatization of the enzymatic products afforded various functional molecules with complete retention of chiral integrity, providing crucial support for the practical application of atropisomeric biaryl amines in the development of organocatalysts and pharmaceuticals. Besides, a borrowing hydrogen cascade system is explored to extend the construction of atropisomeric biaryl amines directly from racemic alcohols. Density functional theory (DFT) calculations and molecular dynamics (MD) simulations are carried out to elucidate the DKR process, selectivity of IR-09, and interactions between the sterically hindered substrates and residues within the enzyme. Our research demonstrated that biocatalysts possess the potential to accept challenging non-native substrates according to specific inherent characteristics and structural flexibility.



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