



XXX National Meeting on Medicinal Chemistry

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

⁷N ¹⁵P ⁶C ⁹F **17**



Book of abstracts



University of Messina
September 13-16, 2026



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



Divisione di Chimica Farmaceutica

WELCOME MESSAGE

On behalf of the Scientific and Organizing Committees, we are pleased to invite you to join the **XXX National Meeting on Medicinal Chemistry (NMMC2026)**, the annual peculiar event of the Divisione di Chimica Farmaceutica (Division of Medicinal Chemistry) of the Società Chimica Italiana (Italian Chemical Society).

NMMC2026, together with the **17th Young Medicinal Chemists Symposium “Nuove Prospettive in Chimica Farmaceutica” (NPCF17)**, represents the best opportunity to share the progress of research and to favor collaborations among medicinal chemists from both academia and industry.

The participants will have the chance to present the results of their studies in the highly stimulating environment of the meeting that will cover the most recent advances belonging to one or more of our peculiar Analytical, Computational and Synthetic Medicinal Chemistry topics, listed in research and therapeutic areas.

The NMMC2026 edition will be organized by the University of Messina. The meeting will start on **September 13th afternoon** with the **Opening Ceremony** at the **Rettorato venue**, and it will continue up to September 16th morning in the conference rooms at the Papardo academic complex belonging to the Università di Messina.

More than **250 colleagues** from academia and industry are expected to join the Meeting with a rich scientific program that will include four plenaries and ten keynote lectures, as well as numerous oral communications and poster presentations.

The meeting will also give the opportunity to release during the Opening Ceremony medal and prizes to the winners selected by the [Divisione di Chimica Farmaceutica](#).

We look forward to welcoming you in Messina!

Prof. Stefano Alcaro (Chair of the Scientific Committee)

Prof. Maria Zappalà (Chair of the Organizing Committee)



XXX

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17th Young Medicinal Chemists' Symposium
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XXX

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EFMC

European Federation
for Medicinal chemistry
and Chemical biology

An independent
association representing
scientific organisations
from more than 25
European countries to
promote contacts and
exchanges between
medicinal chemists and
chemical biologists
in Europe and around
the World.

www.efmc.info



**EFMC
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The EFMC-Young Scientists
Network aims to inspire,
connect, and provide
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XXX

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SCIENTIFIC PROGRAM



XXX

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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica■ SUNDAY 13th Opening Session – Central Building

Aula Magna Rettorato

14:30	REGISTRATION
17:00	OPENING CEREMONY - Chair: Maria Zappalà
	▪ Giovanna Spatari, Rector of the University of Messina ▪ Giovanni Cuda, Rector of the Magna Graecia University of Catanzaro ▪ Federico Basile, Mayor of Messina ▪ Luigi Mondello, President of the Italian Chemical Society ▪ Robert Nisticò, President of the Agenzia Italiana del Farmaco ▪ Stefano Alcaro, President of the Medicinal Chemistry Division of the Italian Chemical Society and Chair of the Scientific Committee ▪ Maria Zappalà, Chair of the Organizing Committee
17:40	Chair: Stefano Alcaro
	SEAL OF THE MEDICINAL CHEMISTRY DIVISION OF THE ITALIAN CHEMICAL SOCIETY ▪ Lucia Bedini, University of Urbino Carlo Bo
	MEDICINAL CHEMISTRY DIVISION OF THE ITALIAN CHEMICAL SOCIETY AWARDS ▪ Mattia Bernetti, University of Urbino Carlo Bo ▪ Vincenzo Maria D'Amore, University of Naples Federico II
	BEST BACHELOR THESIS AWARD "M. BOTTA" ▪ Martina Corsini, Alma Mater Studiorum University of Bologna
	BEST DOCTORAL THESIS AWARDS ▪ FC01: Simona Barone, University of Naples Federico II <i>Histone Deacetylase 6 at the Crossroads of Cancer and Infectious Diseases</i> ▪ FC02: Roberta Bivacqua, University of Palermo <i>Exploration of Thiazole-Based Scaffolds for the Development of Broad-Spectrum Antiviral Agents</i>
18:20	PRATESI MEDAL OF THE MEDICINAL CHEMISTRY DIVISION OF THE ITALIAN CHEMICAL SOCIETY ▪ Gianluca Sbardella, University of Salerno
18:50	OPENING LECTURE ▪ PL01: Fernando Albericio, University of KwaZulu-Natal, Durban, South Africa <i>The Golden Age of Peptides: Emerging Challenges and Future Opportunities</i>
20:00	WELCOME COCKTAIL (Rettorato Courtyard)



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



7 N 15 P 6 C 9 F 17

17th Young Medicinal Chemists' Symposium
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MONDAY 14th Morning Session - Papardo Campus

Aula Magna Vittorio Ricevuto

Chair: Maria Laura Bolognesi

9:00

PL02: Werngard Czechtizky, Independent Researcher
Artificial Intelligence-Powered Platforms for Drug Discovery

Aula Magna Vittorio Ricevuto

Lecture Hall A-T-4

Chairs: Maria Laura Bolognesi / Marco De Vivo

Chairs: Laura De Luca / Rosaria Gitto

10:10

KN01: Giuseppe La Regina
Sapienza University of Rome
Tubulin Targeting Drives Ferroptosis in Cancer

KN02: Tiziano Tuccinardi
University of Pisa
Artificial Intelligence in Drug Discovery: Reading the Small Print

10:40

OC01: Maria Paola Costi
University of Modena e Reggio Emilia
The Discovery of the First in Class Thymidylate Synthase Dimer Disrupters from the Binding Mode at the Dimer Interface to in vivo Studies

OC02: Pasquale Linciano
University of Pavia
Quenching Bacterial Communication: Discovery and Profiling of Quorum Sensing Inhibitors with Antibiofilm and Antivirulence Activity

11:00-11:30 COFFEE BREAK

Aula Magna Vittorio Ricevuto

Lecture Hall A-T-4

Chairs: Maria Laura Bolognesi / Marco De Vivo

Chairs: Laura De Luca / Rosaria Gitto

11:30

KN03: Valentina Gandin
University of Padova
Targeting Copper Metabolism in Cancer for Theranostics: from Copper(I)-Based Small Molecules to Self-Assembled Supramolecular Nanoplatfoms

KN04: Laura Mercolini
Alma Mater Studiorum University of Bologna
Miniaturized Sample Preparation to Drive Innovation in Pharmaceutical Analysis

12:00

OC03: Marta Serafini
University of Turin
Imaging and Targeting Low Oxygen Levels in Tumours

OC06: Giovanna Baron
University of Milan
5-(3',4'-Dihydroxyphenyl)-γ-valerolactone-Sulfate as an Inflammation-Triggered Prodrug for Targeted Nrf2 Activation

12:20

OC04: Michele De Franco
Memorial Sloan Kettering Cancer Center, NY
Cu(I)-Based Antibody-Drug Conjugates: a Novel Platform for Cancer Theranostics

OC07: Federica Blua
University of Turin
Development of a Gut-Restricted NLRP3 Inhibitor for IBD: from Design to in vivo Efficacy



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

12:40	OC05: Valeria Napolitano University of Salerno <i>Untargeted Diversity-Oriented Synthesis (UnDOS) for the Identification of Novel Antitumor Agents: An Integrated Approach of IVS, Bioinformatics and Omics for Targets Deconvolution</i>	OC08: Alessandra Altomare University of Milan <i>A Tunable Carnosine-HNE Michael Adduct Restores Redox-Inflammatory Balance by Modulating the Nrf2-NF-κB Axis</i>
13:00-14:00 LUNCH		
14:00-15:00 POSTER SESSION I AND EXHIBITION		
■ MONDAY 14th - Afternoon Session - Papardo Campus		
	Aula Magna Vittorio Ricevuto	Lecture Hall A-T-4
	Chairs: Roberta Ettari / Maria Zappalà	Chairs: Massimo Dondio / Paolo Grieco
15:00	KN05: Francesco Leonetti University of Bari Aldo Moro <i>The Fascinating Story of N-Adamantyl Anthranilamide Derivatives: Design and Development of Selective CB2R Ligands</i>	KN06: Francesca Spyraakis University of Turin <i>A Precision Medicine Framework for Targeting DNA Polymerase ε in Colorectal Cancer</i>
15:30	OC09: Angela De Simone University of Turin <i>LC-MS Profiling of Histone PTMs in Alzheimer's Disease Mouse Model Astrocytes: toward Early Diagnosis and Targeted Neuroprotection</i>	OC11: Paolo Governa University of Parma <i>Ultrafast Graph Recognition (UGR): a Graph-Based Molecular Similarity Method for Ligand-Based Virtual Screening</i>
15:50	OC10: Alessio Nocentini University of Florence <i>Tuning Multitarget Drug Design Based on Carbonic Anhydrase Modulation for the Treatment of Multifactorial Pathologies</i>	OC12: Bianca Fiorillo University of Naples Federico II <i>Molecular Dynamics Study of ATG13 Ubiquitylation in ULK1 Structural Dynamics and Assembly of Autophagy Initiation Complex</i>
16:15 Excursion to Taormina		



XXX

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Medicinal Chemistry

Messina, Italy - September 13-16, 2026



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Nuove Prospettive in Chimica Farmaceutica

■ TUESDAY 15th - Morning Session - Papardo Campus

Aula Magna Vittorio Ricevuto

Chair: Marco Macchia

9:00

PL03: Elisabetta Chiarparin, Angelini Pharma*Programming Disease Biology with Chemistry: Designing Molecules, Designing Mechanisms*

Aula Magna Vittorio Ricevuto

Lecture Hall A-T-4

Chairs: Marco Macchia / Vincenzo Maria D'Amore

Chairs: Tracey Pirali / Mattia Bernetti

10:10

KN07: Vincenzo Maria D'AmoreUniversity of Naples Federico II (DCF prize)
*From GPCR Activation to Ligand Binding and Kinetics: Integrated Computational Approaches for Medicinal Chemistry***KN08: Mattia Bernetti**University of Urbino Carlo Bo (DCF prize)
Computational Challenges in Structure-Based Drug Design for RNA Targets

10:40

OC13: Elisa UliassiAlma Mater Studiorum University of Bologna
*Harnessing Multi-Target Drug Discovery for Circadian Clock Dysfunction in Alzheimer's Disease***OC14: Giacomo Rossino**University of Pavia
Small Molecules Targeting the HUR-RNA Complexes: an Innovative Strategy to Discover Anticancer Agents

11:00-11:30 COFFEE BREAK

Aula Magna Vittorio Ricevuto

Lecture Hall A-T-4

Chairs: Marco Macchia / Vincenzo Maria D'Amore

Chairs: Tracey Pirali / Mattia Bernetti

11:30

OC15: Elisa PatacchiniSapienza University of Rome
*Unlocking Neuroprotection: Rational Design and Synthesis of $\sigma 1R$ Agonists for Huntington's Disease Treatment***OC17: Luca Piemontese**University of Bari Aldo Moro
From Fungal Metabolites to Multi-Target Ligands: A Nature-Inspired and Green Semi-Synthetic Strategy for Alzheimer's Disease Drug Discovery

11:50

OC16 Emanuele CarosatiUniversity of Trieste
*From Phenotypic Screening to Target Networks: A Polypharmacology-Oriented Approach for Rett Syndrome Therapeutics***OC18: Nicoletta Brindani**Italian Institute of Technology, Genoa
Discovery and Development of Novel Polymerase Eta Inhibitors to Overcome Cancer Drug Resistance



XXX

National Meeting on
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Nuove Prospettive in Chimica Farmaceutica**Aula Magna Vittorio Ricevuto****Chair: Stefano Alcaro****12:10 Sponsor exhibition (Promega)**
12:20 Workshop: Jacopo Gomena, Giorgio Carbone, Matteo Zambra, Italfarmaco
Cutting Through the Hype: Generative Chemistry and Predictive AI Across the Pre-Clinical Drug Discovery Pipeline
13:00-14:00 LUNCH**14:00-15:00 POSTER SESSION II AND EXHIBITION****■ TUESDAY 15th - Afternoon Session - Papardo Campus****Aula Magna Vittorio Ricevuto****Lecture Hall A-T-4****Chairs: Roberta Ettari / Nicola Micale**
15:00 OC19: Valeria Francesconi
 University of Genoa
Design, Synthesis, and Biological Evaluation of Dihydrotriazine-Based Antifolates Against Trypanosoma Brucei
15:20 OC20: Alessandra Corio
 IRBM, Pomezia, Rome
Discovery of IRBM-Z-2: a Potent Allosteric Inhibitor of Zika Virus NS2B-NS3 Protease with Oral Efficacy in Mouse Models
**MENTORING
PROGRAM
DCF
15:00-15:40**
15:40-16:00 COFFEE BREAK**Aula Magna Vittorio Ricevuto****16:00****YOUNG TALKS – RESEARCH IN FIVE MINUTES****Chairs: Marco Franceschin / Morena Miciaccia**

- **FC03: Mysoon Al-Ansari**, King Saud University, Saudi Arabia
Luminal A Breast Cancer Secretome Drives Enterococcus faecalis Toward an Onco-Virulence Phenotype
- **FC04: Giorgia Andreozzi**, University of Naples Federico II
Design and Synthesis of Small Molecules as MicroRNA Modulators in Ischemic Stroke
- **FC05: Marco Banzato**, University of Padova
Design, Synthesis, and Pharmacokinetic Profiling of Fluorinated Reversible N-Alkyl Carbamate Derivatives of Psilocin for Sub-Hallucinogenic Brain Exposure
- **FC06: Angela Belcastro**, University of Milano Bicocca
Synthesis and Biological Evaluation of Novel Covalent Inhibitors of MOK KINASE for the Treatment of Neuroinflammation in Amyotrophic Lateral Sclerosis



XXX

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7 N 15 P 6 C 9 F 17

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

	▪ FC07: Chiara Boero, University of Turin <i>Click Chemistry-Based Strategies for Hypoxia Imaging and Targeted Drug Delivery in Colorectal Cancer Models</i>
	▪ FC08: Jessica Ceramella, University of Calabria <i>A New Series of Carbazole Derivatives with anti-Breast Cancer Properties</i>
	▪ FC09: Marco D'Alì, University of Messina <i>Stereospecificity Membrane Impact of Two Catechins on Red Blood Cells</i>
	▪ FC10: Tommaso Felicetti, University of Perugia <i>Advancing RNA-Targeted Drug Discovery: A Biophysical Platform to Identify MALAT1 Binders as Anti-Melanoma Agents</i>
	▪ FC11: Aurora Gaza, Alma Mater Studiorum University of Bologna <i>Small-Molecule Degradors for Antiparasitic Drug Discovery and Chemical Biology Application</i>
	▪ FC12: Alessandro Greco, Italian Institute of Technology, Genoa <i>DNA Polymerase η Inhibitors Against Cancer Chemoresistance</i>
	▪ FC13: Bianca Martinengo, Alma Mater Studiorum University of Bologna <i>Greening Proteolysis Targeting Chimera Development: Cashew Nutshell Liquid-Based Cereblon Ligands</i>
	▪ FC14: Lorenzo Mattolini, University of Florence <i>Discovery of New Heterocyclic Compounds as Metallo-β-Lactamase Inhibitors to Reverse Antimicrobial Resistance</i>
	▪ FC15: Clara Mocchetti, University of Milan <i>Characterization of Hyaluronic Acid Oligomers by NMR Spectroscopy</i>
	▪ FC16: Matteo Mori, University of Milan <i>Non-Agonist Modulation of PPARγ as a Strategy for Insulin Resistance</i>
	▪ FC17: Alessia Onali, University of Cagliari <i>Novel Thiazolidinone-Isatin Hybrids Potently Inhibit hCA IX and Enhance Doxorubicin-Induced Apoptosis in Hypoxic Glioblastoma Cells</i>
	▪ FC18: Marco Paparella, University of Bari Aldo Moro <i>Multitarget Hybrid Small Molecules for Metal Chelation with Additive Cholinesterase Inhibitory and Antioxidant Properties in Alzheimer's Disease</i>
	▪ FC19: Elena Roggiolani, Alma Mater Studiorum University of Bologna <i>Targeting FYN and GSK-3β to Tackle Neurodegeneration</i>
	▪ FC20: Erica Sanna, University of Cagliari <i>Dual SARS-COV-2 NSP13 Helicase Functions Inhibitors Exhibiting Additive Antiviral Activity as a Proof of Concept for Combination Therapy</i>



XXX

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Medicinal Chemistry

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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



	▪ FC21: Rosa Sparaco, University of Naples Federico II <i>Deflazacort-H₂S Donor Hybrids: A Dual Anti-Inflammatory and Antioxidant Approach for Duchenne Muscular Dystrophy</i>
	▪ FC22: José Starvaggi, University of Messina <i>Development of Novel Peptide-Based Michael Acceptors Targeting Rhodesain of Trypanosoma Brucei Rhodesiense</i>
Aula Magna Vittorio Ricevuto	
18:30	DCF - SCI GENERAL MEETING <i>Assemblea Generale della Divisione di Chimica Farmaceutica</i>
19:30	Bus Tour Laghi di Ganzirri
20:30	SOCIAL DINNER (Giardini di Giano)



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



7 N 15 P 6 C 9 F 17

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

WEDNESDAY 16th Morning Session - Papardo Campus

Aula Magna Vittorio Ricevuto

Chair: Stefano Moro

9:00

PL04: Coral Barbas, Universidad San Pablo CEU, Madrid

From Pathways to Patients: Metabolomics in Modern Drug Discovery

Aula Magna Vittorio Ricevuto

Chairs: Stefano Moro / Orazio Nicolotti

Lecture Hall A-T-4

Chairs: Nunzio Iraci / Rosanna Maccari

10:10

KN09: Jussara Amato

University of Naples Federico II

Protein-Derived Peptides to Target G-Quadruplex DNA: from Molecular Recognition to Anticancer Activity

KN10: Michele De Luca

University of Calabria

From Signals to Knowledge: Machine Learning in Advanced Drug Analysis

10:40

OC21: Michele Coluccia

Sapienza University of Rome

2-Aroyl-5,6-dimethoxybenzofurans and Demethylated Derivatives as Novel Therapeutic Tools Against Glioblastoma

OC23: Simone Carradori

G. d'Annunzio University of Chieti-Pescara

Improving the Knowledge of Human Microbiota: Production, Characterization and Modulation of Novel Carbonic Anhydrases from Probiotic Bacteria

11:00

OC22: Sebastiano Intagliata

University of Catania

Exploiting HO-1 Inhibition Through Mutual Prodrugs Strategy for Improving 5-Fluorouracil Efficacy

OC24: Roberta Rocca

Magna Graecia University of Catanzaro

Beyond the G-Quadruplex: Structure-Based Virtual Screening of the HIV-1 LTR-III Architecture Identifies Novel Antiviral Ligands

11:20-11:50 COFFEE BREAK



XXX

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7 N 15 P 6 C 9 F 17

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Nuove Prospettive in Chimica Farmaceutica■ WEDNESDAY 16th Morning Session - Papardo Campus

	Aula Magna Vittorio Ricevuto	Lecture Hall A-T-4
	Chairs: Morena Miciaccia / Tracey Pirali	Chairs: Nicola Micale / Santo Previti
11:50	OC25: Vincenzo Mazzearella University of Campania Luigi Vanvitelli <i>Expanding The Horizon of Label-Free CTC Detection: Toward a CXCR4-Targeted Plasmonic Optical Fiber Biosensor for Liquid Biopsy Applications</i>	OC28: Giovanna Aquino AREA Science Park, Salerno <i>Upcycling Spinach Processing By-Products into High-Value Bioactives: Green Extraction Optimization and in vivo Photoprotective Activity in Zebrafish Models</i>
12:10	OC26: Isabella Romeo Magna Graecia University of Catanzaro <i>Rational Design, Synthesis and Structural Mechanism of MSP20, a Novel TRPV1 Agonist Endowed with Long-Lasting Analgesic Action</i>	OC29: Salvatore Mirabile University of Messina <i>Designing Dual-Action Luminescent Inhibitors of Tyrosinase: Synthesis and Biological Evaluation</i>
12:30	OC27: Daniela Trisciuzzi University of Bari Aldo Moro <i>Exploring Ligandable Pockets of 3D OncoPPI Networks for Improving Protein Inhibition and Degradation Strategies</i>	OC30: Federico Paccioia University of Perugia <i>Structural Determinants Governing Ligand-Binding Domain Opening of the DAF-12 Receptor</i>
Aula Magna Vittorio Ricevuto		
	Chairs: Stefano Alcaro / Maria Zappalà	
13:00	POSTER PRIZES supported by Chemistry Europe	
13:20	CLOSING REMARKS	



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



Divisione di Chimica Farmaceutica

TABLE OF CONTENTS



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



PLENARY LECTURES	1
PL01 - THE GOLDEN AGE OF PEPTIDES: EMERGING CHALLENGES AND FUTURE OPPORTUNITIES	
Fernando Albericio	2
PL02 - ARTIFICIAL INTELLIGENCE POWERED PLATFORMS FOR DRUG DISCOVERY	
Werngard Czechtizky	3
PL03 - PROGRAMMING DISEASE BIOLOGY WITH CHEMISTRY: DESIGNING MOLECULES, DESIGNING MECHANISMS	
Elisabetta Chiarparin	4
PL04 - FROM PATHWAYS TO PATIENTS: METABOLOMICS IN MODERN DRUG DISCOVERY	
Coral Barbas	5
KEYNOTE LECTURES	6
KN01 - TUBULIN TARGETING DRIVES FERROPTOSIS IN CANCER	
Giuseppe La Regina	7
KN02 - ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY: READING THE SMALL PRINT	
Tiziano Tuccinardi	8
KN03 - TARGETING COPPER METABOLISM IN CANCER FOR THERANOSTICS: FROM COPPER(II)-BASED SMALL MOLECULES TO SELF-ASSEMBLED SUPRAMOLECULAR NANOPLATFORMS	
Valentina Gandin	9
KN04 - MINIATURIZED SAMPLE PREPARATION TO DRIVE INNOVATION IN PHARMACEUTICAL ANALYSIS	
Laura Mercolini	10
KN05 - THE FASCINATING STORY OF N-ADAMANTYL ANTHRANILAMIDE DERIVATIVES: DESIGN AND DEVELOPMENT OF SELECTIVE CB2R LIGANDS	
Francesco Leonetti	11
KN06 - A PRECISION MEDICINE FRAMEWORK FOR TARGETING DNA POLYMERASE E IN COLORECTAL CANCER	
Francesca Spyraakis	12
KN07 - FROM GPCR ACTIVATION TO LIGAND BINDING AND KINETICS: INTEGRATED COMPUTATIONAL APPROACHES FOR MEDICINAL CHEMISTRY	
D'Amore V.M., Raniolo S., Conflitti P., Di Maro S., Leuti A., Maccarrone M., Marinelli L., Di Leva F.S., Limongelli V.	13
KN08 - COMPUTATIONAL CHALLENGES IN STRUCTURE-BASED DRUG DESIGN FOR RNA TARGETS	
Bernetti M., Aguti R., Bosio S., Masetti M., Cavalli A.	14
KN09 - PROTEIN-DERIVED PEPTIDES TO TARGET G-QUADRUPLEX DNA: FROM MOLECULAR RECOGNITION TO ANTICANCER ACTIVITY	
Jussara Amato	15
KN10 - FROM SIGNALS TO KNOWLEDGE: MACHINE LEARNING IN ADVANCED DRUG ANALYSIS	
Michele De Luca	16
ORAL COMMUNICATIONS	17
OC01 - THE DISCOVERY OF THE FIRST IN CLASS THYMIDYLATE SYNTHASE DIMER DISRUPTERS FROM THE BINDING MODE AT THE DIMER INTERFACE TO IN VIVO STUDIES	
Costi M.P., Aiello D., Ponterini G., D'Arca D., Marverti G., Tagliazucchi L., Moschella M., Lamesta M., Malpezzi G., Venturelli A., Remo G., Pacifico S., Pozzi C.	18
OC02 - QUENCHING BACTERIAL COMMUNICATION: DISCOVERY AND PROFILING OF QUORUM SENSING INHIBITORS WITH ANTIBIOFILM AND ANTIVIRULENCE ACTIVITY	
Linciano P., Milli G., Menegussi Bellan E., Pagano K., Ragona L., Pietrocola G., Collina S.	19



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica**OC03 - IMAGING AND TARGETING LOW OXYGEN LEVELS IN TUMOURS**

Boumya S., Boero C., Di Addario M., Trusolino L., Serafini M.20

OC04 - CU(I)-BASED ANTIBODY-DRUG CONJUGATES: A NOVEL PLATFORM FOR CANCER THERANOSTICS

De Franco M., Forner M., Lewis J.S., Gandin V.21

OC05 - UNTARGETED DIVERSITY-ORIENTED SYNTHESIS (UNDOS) FOR THE IDENTIFICATION OF NOVEL ANTITUMOR AGENTS: AN INTEGRATED APPROACH OF IVS, BIOINFORMATICS AND OMICS FOR TARGETS DECONVOLUTION

Napolitano V., Ciaglia T., Miranda M.R., Smaldone G., Di Matteo F., Sommella E.M., Ligresti A., Bifulco G., Lauro G., Campiglia P., Vestuto V., Bertamino A.22

OC06 - 5-(3',4'-DIHYDROXYPHENYL)-L-VALEROLACTONE-SULFATE AS AN INFLAMMATION-TRIGGERED PRODRUG FOR TARGETED NRF2 ACTIVATION

Della Vedova L., Gado F., Ferrisi R., Mauri A., Taheribavilyaei R., Messinese S., Bassi A., Manzi S., Altomare A., Dallanoe C., Aldini G., Baron G.23

OC07 - DEVELOPMENT OF A GUT-RESTRICTED NLRP3 INHIBITOR FOR IBD: FROM DESIGN TO IN VIVO EFFICACY

Blua F., Pierucci C., Angelini S., Boccato F., Marini E., Pellegrini C., Bertinaria M.24

OC08 - A TUNABLE CARNOSINE-HNE MICHAEL ADDUCT RESTORES REDOX-INFLAMMATORY BALANCE BY MODULATING THE NRF2-NF-KB AXIS

Altomare A., Baron G., Gado F., Della Vedova L., Ferrario G., Davani L., Gilardoni E., Ferrisi R., Mocchetti C., Siracusa R., D'Amico R., Di Paola R., Dallanoe C., Impellizzeri D., Aldini G.25

OC09 - LC-MS PROFILING OF HISTONE PTMS IN ALZHEIMER'S DISEASE MOUSE MODEL ASTROCYTES: TOWARD EARLY DIAGNOSIS AND TARGETED NEUROPROTECTION

De Simone A., Esposito E., Grolla A., Cavallo M., Casali C., Lim D., Tapella L., Naldi M., Fiori J.26

OC10 - TUNING MULTITARGET DRUG DESIGN BASED ON CARBONIC ANHYDRASE MODULATION FOR THE TREATMENT OF MULTIFACTORIAL PATHOLOGIES

Nocentini A.27

OC11 - ULTRAFast GRAPH RECOGNITION (UGR): A GRAPH-BASED MOLECULAR SIMILARITY METHOD FOR LIGAND-BASED VIRTUAL SCREENING

Governa P., Forli S.28

OC12 - MOLECULAR DYNAMICS STUDY OF ATG13 UBIQUITYLATION IN ULK1 STRUCTURAL DYNAMICS AND ASSEMBLY OF AUTOPHAGY INITIATION COMPLEX

Fiorillo B., Moraca F., Senatore E., Bianco A.G., Feliciello A., Catalanotti B.29

OC13 - HARNESSING MULTI-TARGET DRUG DISCOVERY FOR CIRCADIAN CLOCK DYSFUNCTION IN ALZHEIMER'S DISEASE

Kampasis D., Castellino I., Huang X., Faiyaz K.I., Bartolini M., Albani D., Musilek K., Guedes R., Bolognesi M.L., Uliassi E.30

OC14 - SMALL MOLECULES TARGETING THE HUR-RNA COMPLEXES: AN INNOVATIVE STRATEGY TO DISCOVER ANTICANCER AGENTS

Rossino G., Garbagnoli M., Fontana A., Cavassi E., Rossi D., Linciano P., Vaccari M.E., Bedeschi M., Ambrosio F.A., Costa G., Alcaro S., Gado I., Vasile F., Tesei A., Collina S.31

OC15 - UNLOCKING NEUROPROTECTION: RATIONAL DESIGN AND SYNTHESIS OF $\Sigma 1R$ AGONISTS FOR HUNTINGTON'S DISEASE TREATMENT

Patacchini E., Cosconati S., Ciruela F., Keserű G.M., Kiss D.J., Esposito G., Madia V.N., Messori A., Saccoliti F., Di Santo R., Costi R.32

OC16 - FROM PHENOTYPIC SCREENING TO TARGET NETWORKS: A POLYPHARMACOLOGY-ORIENTED APPROACH FOR RETT SYNDROME THERAPEUTICS

Tongiori E., Berutto V., Ciraci V., Prado Romero D.L., Gualandi N., Roggero O.M., Carosati E.33



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica**OC17 - FROM FUNGAL METABOLITES TO MULTI-TARGET LIGANDS: A NATURE-INSPIRED AND GREEN SEMI-SYNTHETIC STRATEGY FOR ALZHEIMER'S DISEASE DRUG DISCOVERY**

Leuci R., Paparella M., Chaves S., Gialluisi K., Carrieri A., Gambacorta L., Spreitzer I., Roselli V., Laghezza A., Ferrara M., Cerini M., Perrone G., Santos M.A., Piemontese L.34

OC18 - DISCOVERY AND DEVELOPMENT OF NOVEL POLYMERASE ϵ TA INHIBITORS TO OVERCOME CANCER DRUG RESISTANCE

Brindani N., Greco A., Pellegrino F., Zuffa R., La Serra M.A., De Vivo M.35

OC19 - DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF DIHYDROTRIAZINE-BASED ANTIFOLATES AGAINST *TRYPANOSOMA BRUCEI*

Francesconi V., Carbone A., Aiello D., Pozzi C., Santarem N., Cordeiro Da Silva A., Costi M.P., Tonelli M.36

OC20 - DISCOVERY OF IRBM-Z-2: A POTENT ALLOSTERIC INHIBITOR OF ZIKA VIRUS NS2B-NS3 PROTEASE WITH ORAL EFFICACY IN MOUSE MODELS

Corio A., Montalbetti C., Paonessa G., Ontoria J., Alli C., Missineo A., Quotadamo A., Ferrigno F., Ievoli G., Vasile S., Bisbocci M., Conti S., Veneziano M., Proto G., Orsatti L., Toniatti C., Torrente E.37

OC21 - 2-AROYL-5,6-DIMETHOXYBENZOFURANS AND DEMETHYLATED DERIVATIVES AS NOVEL THERAPEUTIC TOOLS AGAINST GLIOBLASTOMA

Coluccia M., Arrighi F., Vernile S., Buttitta G., Guglielmi P., Chimenti P., Granese A., Secci D.38

OC22 - EXPLOITING HO-1 INHIBITION THROUGH MUTUAL PRODRUGS STRATEGY FOR IMPROVING 5-FLUOROURACIL EFFICACY

Mocka S., Salerno L., Pittalà V., Modica M.N., Romeo G., Consoli V., Sorrenti V., Sodano F., Ambrosio M.R., Fiory F., Magli E., Intagliata S.39

OC23 - IMPROVING THE KNOWLEDGE OF HUMAN MICROBIOTA: PRODUCTION, CHARACTERIZATION AND MODULATION OF NOVEL CARBONIC ANHYDRASES FROM PROBIOTIC BACTERIA

Paoletti N., Carradori S., De Luca V., Bonardi A., Gratteri P., Supuran C.T., Capasso C.40

OC24 - BEYOND THE G-QUADRUPLEX: STRUCTURE-BASED VIRTUAL SCREENING OF THE HIV-1 LTR-III ARCHITECTURE IDENTIFIES NOVEL ANTIVIRAL LIGANDS

Rocca R., Cannistrà M.S.F., Gargano A., Nadai M., Pirota V., Fracchioni G., Frasson I., Doria F., Alcaro S.41

OC25 - EXPANDING THE HORIZON OF LABEL-FREE CTC DETECTION: TOWARD A CXCR4-TARGETED PLASMONIC OPTICAL FIBER BIOSENSOR FOR LIQUID BIOPSY APPLICATIONS

Mazzarella V., Arcadio F., Trotta A.M., Marzano C., Cosconati S., Zeni L., Cennamo N., Scala S., Di Maro S.42

OC26 - RATIONAL DESIGN, SYNTHESIS AND STRUCTURAL MECHANISM OF MSP20, A NOVEL TRPV1 AGONIST ENDOWED WITH LONG-LASTING ANALGESIC ACTION

Romeo I., Neuberger A., Aiello F., Alekseev A., Maramai S., Pessina F., Vagaggini C., Poggialini F., Dreassi E., Frosini M., Schiano Moriello A., De Petrocellis L., Morace A.M., Belardo C., Perrone M., Bonsale R., Luongo L., Maione S., Talyzina I.A., Brizzi A., Sobolevsky A.I., Alcaro S., Artese A.43

OC27 - EXPLORING LIGANDABLE POCKETS OF 3D ONCOPPI NETWORKS FOR IMPROVING PROTEIN INHIBITION AND DEGRADATION STRATEGIES

Trisciuzzi D., Nicolotti O., Cruciani G., Menna G., Siragusa L.44

OC28 - UPCYCLING SPINACH PROCESSING BY-PRODUCTS INTO HIGH-VALUE BIOACTIVES: GREEN EXTRACTION OPTIMIZATION AND IN VIVO PHOTOPROTECTIVE ACTIVITY IN ZEBRAFISH MODELS

Aquino G., Pepe G., Miranda M.R., Vestuto V., Campiglia P.45

OC29 - DESIGNING DUAL-ACTION LUMINESCENT INHIBITORS OF TYROSINASE: SYNTHESIS AND BIOLOGICAL EVALUATION

Mirabile S., Bonaccorsi P.M., Monforte M., Centorrino L., D'Angelo V., Germanò M.P., Gitto R., De Luca L., Pontoriero M., Scumaci D., Gangemi C.M.A.46



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

OC30 - STRUCTURAL DETERMINANTS GOVERNING LIGAND-BINDING DOMAIN OPENING OF THE DAF-12 RECEPTOR	
Paccoia F., Passeri D., Goracci L., Carotti A., Gioiello A.	47
FLASH COMMUNICATIONS	48
FC01 - HISTONE DEACETYLASE 6 AT THE CROSSROADS OF CANCER AND INFECTIOUS DISEASES	
Barone S., Bello I., Guadagni A., Cerchia C., Schäker-Hübner L., Baptiste M., Filocamo G., Panza E., Buommino E., Hansen F.K., Summa V., Brindisi M.	49
FC02 - EXPLORATION OF THIAZOLE-BASED SCAFFOLDS FOR THE DEVELOPMENT OF BROAD-SPECTRUM ANTIVIRAL AGENTS	
Bivacqua R., Romeo I., Emmolo R., Barreca M., Raimondi M.V., Spanò V., Corona A., Alcaro S., Naesens L., Andrei G., Tramontano E., Montalbano A., Barraja P.	50
FC03 - LUMINAL A BREAST CANCER SECRETOME DRIVES <i>ENTEROCOCCUS FAECALIS</i> TOWARD AN ONCO-VIRULENCE PHENOTYPE	
Al-Ansari M., Mahmood S., Alwan M.	51
FC04 - DESIGN AND SYNTHESIS OF SMALL MOLECULES AS MICRORNA MODULATORS IN ISCHEMIC STROKE	
Andreozzi G., Pignataro G., Patil R., Licastro E., Viscardi V., Vertuccio S., Severino B., Kaczor A., Santagada V., Fiorino F.	52
FC05 - DESIGN, SYNTHESIS, AND PHARMACOKINETIC PROFILING OF FLUORINATED REVERSIBLE N-ALKYL CARBAMATE DERIVATIVES OF PSILOCIN FOR SUB-HALLUCINOGENIC BRAIN EXPOSURE	
Banzato M., Colognesi M., Lucatello L., Comai S., Pasut G., Capolongo F., Orian L., Biasutto L., Signor A., Gabbia D., Manfredi P.L., De Martin S., Mattarei A.	533
FC06 - SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL COVALENT INHIBITORS OF MOK KINASE FOR THE TREATMENT OF NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS	
Belcastro A., Tasneem S., Romero A., Vertemara J., Silvera L., Faldrini M., Barbieri B., Najmanovich R., Roodveldt C., De Gioia L., Peri F.	54
FC07 - CLICK CHEMISTRY-BASED STRATEGIES FOR HYPOXIA IMAGING AND TARGETED DRUG DELIVERY IN COLORECTAL CANCER MODELS	
Boero C., Di Addario M., De Luigi E., Boumya S., Lazzarato L., Serafini M.	55
FC08 - A NEW SERIES OF CARBAZOLE DERIVATIVES WITH ANTI-BREAST CANCER PROPERTIES	
Ceramella J., Iacopetta D., Rosano C., Dallemagne P., Rochais C., Sinicropi M.S.	56
FC09 - STEREOSPECIFICITY MEMBRANE IMPACT OF TWO CATECHINS ON RED BLOOD CELLS	
D'Alì M., Putaggio S., Russo A., Patanè G.T., Caruso D., Giofrè S.V., Tellone E., Iraci N.	57
FC10 - ADVANCING RNA-TARGETED DRUG DISCOVERY: A BIOPHYSICAL PLATFORM TO IDENTIFY MALAT1 BINDERS AS ANTI-MELANOMA AGENTS	
Felicetti T., Rigo R., Coelho Dias I.F., Cozzaglio M., Casciari M., Mucenji E., Sancineto L., Tabarrini O., Sissi C., Massari S.	58
FC11 - SMALL-MOLECULE DEGRADERS FOR ANTIPARASITIC DRUG DISCOVERY AND CHEMICAL BIOLOGY APPLICATIONS	
Gaza A., Diamanti E., Uliassi E., Bolognesi M.L., de Koning H.	59
FC12 - DNA POLYMERASE H INHIBITORS AGAINST CANCER CHEMORESISTANCE	
Greco A., Pellegrino F., Zuffa R., La Serra M., Brindani N., De Vivo M.	60
FC13 - GREENING PROTEOLYSIS TARGETING CHIMERA DEVELOPMENT: CASHEW NUTSHELL LIQUID-BASED CEREBLON LIGANDS	
Martinengo B., Diamanti E., Salerno A., Napolitano V., Berisio R., Bolognesi M.L.	61
FC14 - DISCOVERY OF NEW HETEROCYCLIC COMPOUNDS AS METALLO-β-LACTAMASE INHIBITORS TO REVERSE ANTIMICROBIAL RESISTANCE	
Mattolini L., Braconi L., Docquier J.D., Giovannoni M.P., Crocetti L., Teodori E.	62



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica**FC15 - CHARACTERIZATION OF HYALURONIC ACID OLIGOMERS BY NMR SPECTROSCOPY**

Mocchetti C., Ferrisi R., Nava D., Messinese S., Cazzaniga A., Manzi S., Fumagalli G., Rossitto S., Vaccaro S., Inturri R., Soato M., Altomare A., Baron G., Aldini G., Dallanoce C.63

FC16 - NON-AGONIST MODULATION OF PPAR γ AS A STRATEGY FOR INSULIN RESISTANCE

Cazzaniga G., Capelli D., Montanari R., Laghezza A., Loiodice F., Fassi E.M.A., Grazioso G., Rinaldi F., Calleri E., Villa S., Crestani M., Meneghetti F., Villa S., Mori M.64

FC17 - NOVEL THIAZOLIDINONE-ISATIN HYBRIDS POTENTLY INHIBIT hCA IX AND ENHANCE DOXORUBICIN-INDUCED APOPTOSIS IN HYPOXIC GLIOBLASTOMA CELLS

Onali A., Guarnieri L., Bosco F., Lupia A., Sanna E., Demuru L., Atzeni G., Meleddu R., Cottiglia F., Supuran C.T., Distinto S., Maccioni E.65

FC18 - MULTITARGET HYBRID SMALL MOLECULES FOR METAL CHELATION WITH ADDITIVE CHOLINESTERASE INHIBITORY AND ANTIOXIDANT PROPERTIES IN ALZHEIMER'S DISEASE

Paparella M., Chaves S., Leuci R., Roselli V., Cerini M., Carrieri A., Tortorella P., Loiodice F., Laghezza A., Santos M.A., Piemontese L.66

FC19 - TARGETING FYN AND GSK-3 β TO TACKLE NEURODEGENERATION

Roggiani E., Basagni F., Penna I., Russo D., Scarpelli R., Falchi F., Minarini A., Rosini M.67

FC20 - DUAL SARS-COV-2 NSP13 HELICASE FUNCTIONS INHIBITORS EXHIBITING ADDITIVE ANTIVIRAL ACTIVITY AS A PROOF OF CONCEPT FOR COMBINATION THERAPY

Sanna E., Distinto S., Corona A., Lupia A., Onali A., Emmolo R., Maloccu S., Crespan E., Bavagnoli L., Lodola C., Schlich M., Podda E., Meleddu R., Secci D., Cottiglia F., Malune P., Esposito F., Scognamiglio S., Fernandes C., Borges F., Meier C., Tramontano E., Maccioni E.68

FC21 - DEFLAZACORT-H₂S DONOR HYBRIDS: A DUAL ANTI-INFLAMMATORY AND ANTIOXIDANT APPROACH FOR DUCHENNE MUSCULAR DYSTROPHY

Sparaco R., Cinque P., Citi V., Martelli A., Calderone V., Bucci M., Cirino G., Scognamiglio A., Corvino A., Perissutti E., Vellecco V., Frecentese F.69

FC22 - DEVELOPMENT OF NOVEL PEPTIDE-BASED MICHAEL ACCEPTORS TARGETING RHODESAIN OF TRYPANOSOMA BRUCEI RHODESIENSE

Starvaggi J., Di Chio C., Previti S., Cosconati S., Zappalà M., Ettari R.70

P O S T E R S71**P001 - DESIGN AND SYNTHESIS OF A LIBRARY OF THALIDOMIDE-BASED PROTEOLYSIS TARGETING CHIMERAS (PROTACS) AS ANTIVIRAL AGENTS**

Corsini M., Martinengo B., Diamanti E., Piazza F., Bolognesi M.L.72

P002 - DEVELOPMENT OF INNOVATIVE COMPOUNDS TARGETING SARS-COV-2 NSP13

Albano A., Zarbo L., Ruggieri G., Cara E., Patacchini E., Madia V.N., Saccoliti F., Messori A., Marcorelli B., Emmolo R., Corona A., De Santis R., Amoroso A., Lista F., Loregian A., Tramontano E., Costi R., Di Santo R.73

P003 - DESIGNING A NEW-GENERATION OF GLS1 ALLOSTERIC INHIBITORS BASED ON IN SILICO FRAGMENT-BASED STRATEGY

Allahi S., Trombetti G.A., Poggialini F., Vagaggini C., Dreassi E., Tonelli M., Francesconi V., Schenone S., Carbone A., Fossa P., D'Ursi P.74

P004 - INHIBITION OF FTSJ1 BY 1,2,4-TRIAZOLE DERIVATIVES AS A MECHANISM FOR TRANSLATIONAL READTHROUGH: AN INTEGRATED COMPUTATIONAL AND EXPERIMENTAL STUDY

Roomi M.S., Vitale E., Ricci D., Varrica R., Fiduccia I., Pace A., Lentini L., Pibiri I., Culletta G., Almerico A.M., Tutone M.75

P005 - DEVELOPMENT OF PKF3B KINASE COVALENT INHIBITORS WITH ANTITUMOR ACTIVITY

Antonini G., Mainetti A., Fiore A., Scarano A., Sicuro L., Faggiano S., Celesia A., Mollica L., Tamborini L., Donadelli M., Conti P., Bruno S., Borsari C.76



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P006 - EFFICIENT SYNTHESIS OF THE KINASE INHIBITOR NVS-PI3-4 USING FLOW CHEMISTRY, MICROWAVE IRRADIATION, AND IMMOBILIZED REAGENTS	
Antonini G., Vicinanza S., Mainetti A., Conti P., Tamborini L., Borsari C.	77
P007 - FROM MOLECULAR DESIGN TO NEUROPROTECTION: A JOURNEY THROUGH BENZO[B]THIOPHENE-BASED MAO-B INHIBITORS	
Arrighi F., Berrino E., Guglielmi P., Carradori S., Marconi G.D., Pizzicannella J., Guarnieri S., Tuccinardi T., Poli G., Pepi F., Troiani A., Salvitti C., Di Noi A., Coluccia M., Buttitta G., Pontecorvi V., Granese A., Chimenti P., Secci D., Petzer A., Petzer J., Diomedea F.	78
P008 - REPURPOSING MEDICINAL CHEMISTRY CONCEPTS FOR TARGET-BASED DISCOVERY OF <i>ANTI-XYLELLA FASTIDIOSA</i> AGROCHEMICALS	
Astolfi A., De Souza-Neto R.R., Caliendo R., Amoia S.S., Capelli D., Montanari R., Mangini V., Sciancalepore A.G., Caliendo R., Saldarelli P., Sabatini S., Giampetruzzi A., Barreca M.L.	79
P009 - FIRST-IN-CLASS SPIROOXINDOLE-SULFONAMIDE HYBRIDS AS TRIPLE-TARGET EGFR/CDK2/CA IX/XII INHIBITORS: POTENT ANTI-BREAST CANCER AGENTS WITH MULTIMODAL ACTION	
Alsubaie S.A., Ali M., Alayyaf A.A., Shawish I., Islam M.S., Nafie M.S., Angeli A., Carta F., Supuran C.T., El-Fahama A., Barakat A.	80
P010 - MELATONIN-RELATED COMPOUNDS WITH ANTIOXIDANT AND NEUROPROTECTIVE PROPERTIES	
Barbarossa A., Carrieri A., Macchia E., Porfido R. A., Leoni C., Petrosillo G., Carocci A.	81
P011 - EXPLORING DISULFIDE BRIDGE AS A TOOL TO IMPROVE PIOGLITAZONE'S NEUROPROTECTIVE POTENTIAL: TOWARD THE DEVELOPMENT OF PROLONGED-ACTING MAO-B/PPARγ MODULATORS	
Basagni F., Di Paolo M.L., Laghezza A., Cozza G., Piazzola F., Facci L., Marcolin E., Roggiolani E., Piemontese L., Minarini A., Zusso M., Dalla Via L., Rosini M.	82
P012 - INTEGRATED MACHINE LEARNING AND STRUCTURE-BASED DISCOVERY OF TANKYRASE 1 INHIBITORS	
Bilotta M., Gargano A., Rocca R., Alcaro S.	83
P013 - B.R.E.A.S.T.: AN INTERPRETABLE MACHINE LEARNING FRAMEWORK FOR PROTEOMICS-DRIVEN THERAPY OUTCOME PREDICTION IN BREAST CANCER AND TRIPLE-NEGATIVE BREAST CANCER	
Bono A., La Monica G., Alamia F., Tocco D., Lauria A., Martorana A.	84
P014 - CATHEPSIN-B ACTIVABLE PRODRUGS OF HISTONE DEACETYLASE INHIBITORS	
Campagna E., Papulino C., Altucci L., Di Maro S., Benedetti R.	85
P015 - TRANSCRIPTIONAL REPRESSION OF HIV-1 VIA SMALL-MOLECULE STABILIZATION OF THE LTR-III G-QUADRUPLEX	
Cannistrà M.S.F., Rocca R., Gargano A., Frasson I., Doria F., Ding E., Contessoto V., Onuchic J.N., Alcaro S.	86
P016 - IDENTIFICATION OF NOVEL NITROGEN-BASED DERIVATIVES TARGETING SARS-COV-2 RdRp	
Cara E., Albano A., Zarbo L., Ruggieri G., Patacchini E., Madia V.N., Saccoliti F., Messori A., Scipione L., Malune P., Nieddu S., Esposito F., Tramontano E., Costi R., Di Santo R.	87
P017 - GRIPkit: A COMPREHENSIVE COMPUTATIONAL SUITE FOR THE CHARACTERIZATION AND QUANTIFICATION OF NON-COVALENT INTERACTIONS IN PROTEIN-LIGAND COMPLEXES	
Carbone G., Manenti A.D., Teruzzi G., Sandrone G., Rovelli G., Oliva M.F., Greco C., Steinkuhler C., Cosentino U.R.	88
P018 - PHENOTHIAZINE DERIVATIVES ENDOWED WITH ANTIOXIDANT ACTIVITY AS MULTIFUNCTIONAL COMPOUNDS IN NEURODEGENERATIVE DISEASE	
Carrieri A., Barbarossa A., Porfido R.A., Deruvo C., De Candia M., Carocci A.	89
P019 - FROM POMEGRANATE JUICE TO BIOACTIVE EXTRACTS: PROCESSING-DEPENDENT PHYTOCHEMICAL MODULATION AND NEUROPROTECTIVE POTENTIAL OF RELATED NUTRACEUTICALS	
Cesa S., Zengin G., Gallorini M., Mannina L., Carradori S.	90



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P020 - COUMARIN- AND DIPICOLYLAMINE-TERPENOID HYBRIDS AS SELECTIVE CARBONIC ANHYDRASES IX AND XII INHIBITORS: MECHANISTIC IN-SIGHTS AND SELECTIVE ANTI-MYELOMA POTENTIAL	
Angeli A., Amodio N., Valentino I., Gentile M., D'Agostino I., Moi D., Supuran C.T., Carradori S.	91
P021 - DISCOVERY OF SELECTIVE MALAT1 TRIPLE HELIX LIGANDS THROUGH INTEGRATED BIOCHEMICAL SCREENING	
Casciari M., Duca M.	92
P022 - COMPUTATIONAL AND KINETIC ANALYSIS OF PSMA RADIOLIGANDS TO PREDICT IN VIVO KINETIC PROFILE	
Casini B., Dighero E., Arrigoni F., Sambuceti G.M., Manconi A., Trombetti G.A., Riondato M., Bauckneht M., D'Ursi P., Fossa P.	93
P023 - COMPUTATIONAL DISCOVERY OF DUAL HUMAN AND MUSHROOM TYROSINASE INHIBITORS FROM NATURAL SOURCES USING MACHINE LEARNING TECHNIQUES	
Centorrino L., Pitasi G., De Luca L.	94
P024 - MOLECULAR DOCKING OF ANTI-MELANOGENIC AND FLUORESCENT NATURAL PRODUCT-INSPIRED DERIVATIVES AFFECTING TYROSINASE ACTIVITY	
Centorrino L., Monforte M., Mirabile S., Pontoriero M., Bonaccorsi P.M., Calderaro A., D'Angelo V., De Luca L., Germanò M.P., Gitto R., Patanè G.T., Putaggio S., Scumaci D., Gangemi C.M.A.	95
P025 - EVALUATION OF THE ANTITUMOR ACTIVITY OF THE AYURVEDIC MIXTURE TRIPHALA	
Ceramella J., Iacopetta D., Marra M., Barbo G., Tenuta A.C., Gattuso A., Sicari V., Loizzo M.R., Tundis R., Sinicropi M.S.	96
P026 - DEVELOPMENT OF LIGHT-STABLE DICLOFENAC SODIUM CARRIERS THROUGH A SUSTAINABLE MEMBRANE-BASED APPROACH	
Chieffallo M., Piacentini E., Bazzarelli F., Giorno L., Fuoco A., Occhiuzzi M.A., De Luca M., Grande F., Ioele G.	97
P027 - PYRAZOLYL-THIOUREA DERIVATIVES AS SIRT2 INHIBITORS: STRUCTURAL DIVERSIFICATION AND SAR STUDIES	
Chiocca A., Lusardi M., Astigiano C., Cichero E., Spallarossa A., Ponassi M., Bruzzzone S., Brullo C.	98
P028 - A NOVEL INDOLE-BASED MULTI-TARGET THERAPEUTIC AGENT TARGETING HCA IX/XII, WNT/β CATENIN PATHWAY, AND P-gp	
Colla C., Rotili G., Santelli M., Coluccia A., La Regina G., Silvestri R.	99
P029 - NEW CB2 DUALSTERIC LIGANDS FOR THE TREATMENT OF MULTIPLE SCLEROSIS	
Corallo A.A., Galeotti N., Manetti F., Pellati F., Governa P., Mugnaini C.	100
P030 - DISCOVERY OF A SELECTIVE INDOLE-BASED LITR INHIBITOR FOR ANTI-LEISHMANIA THERAPY THROUGH A ONE HEALTH-GUIDED MULTISCALE COMPUTATIONAL FRAMEWORK	
Curcio A., Pavia G., Rocca R., Brufani V., Exertier C., Ilari A., Marascio N., Quirino A., Artese A., Matera G., Alcaro S.	101
P031 - TOWARDS A COMPREHENSIVE DE NOVO DESIGN APPROACH: THE DISCOVERY OF P38:MK2 MOLECULAR GLUES	
D'Arrigo G., Bhat S., Bos P., Kaushik A.	102
P032 - STRUCTURE-ACTIVITY OF B-LACTAM AND B-LACTAMASE INHIBITOR COMBINATIONS: ASSESSING THE IMPACT OF AMOXICILLIN SHORTAGES IN ITALY (2020-2024)	
Irrera P., Frattima G., Ardizzone A., Previti S., Ettari R., Esposito E.	103
P033 - INVESTIGATING SARS OF NOVEL 8-BENZYLOXY-γ-CARBOLINE DERIVATIVES AS MULTITARGET-DIRECTED LIGANDS FOR NEURODEGENERATIVE DISEASES	
Deruvo C., Samarelli F., Gesmundo D., Lasaracina N., Miniero V., Carrieri A., Catto M., Nicolotti O., Altomare C.D., De Candia M.	104
P034 - DEVELOPMENT OF NOVEL CHALCONE DERIVATIVES: DESIGN, SYNTHESIS AND ANTIPROLIFERATIVE EVALUATION	
Di Chio C., Totaro N., Paterniti I., Esposito E., Previti S., Zappalà M., Ettari R.	105
P035 - ASYMMETRIC CHALCONES AS RHODESAIN INHIBITORS: EXPLORING COMBINATION STRATEGIES WITH CURCUMIN	
Di Chio C., Starvaggi J., Natale B., Previti S., Cosconati S., Zappalà M., Ettari R.	106



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



7 N 15 P 6 C 9 F 17

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica**P036 - DESIGN, SYNTHESIS, IN VITRO AND IN VIVO LIPIDOMIC PROFILING OF A NOVEL ADAMANTYLUREIDO-BENZYLAMIDE ANILINE AS FLAP/SEH DUAL INHIBITOR**

Di Dio A., Ciaglia T., D'Avino D., Jordan P.M., Di Micco S., Musella S., Di Sarno V., Smaldone G., Di Matteo F., Napolitano V., Pepe G., Sommella E.M., Campiglia P., Ostacolo C., Werz O., Rossi A., Bertamino A., Manfra M.107

P037 - BIPHENYLAMIDE-BASED DUAL SOCE/DHODH INHIBITORS FOR DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS: HIT-TO-LEAD OPTIMIZATION AND EX VIVO VALIDATION IN PATIENT-DERIVED PBMCS

Di Martino R.M.C., Muschitiello C., Gioiello L., Gallo E., Elisi G.M., Alberti M., Quartuccio L., Girotto G., Miggiano R., Azzarone L., Bottegoni G., Riva B., Pirali T.108

P038 - DESIGN, SYNTHESIS, AND FUNCTIONAL ASSESSMENT OF OXAZOLOPYRIMIDINES AS MULTITARGET ABC TRANSPORTER INHIBITORS

Di Matteo F., Stefan K., Musella S., Ciaglia T., Di Micco S., Gopakumar G., Bertamino A., Campiglia P., Stefan S.M., Ostacolo C.109

P039 - IN-DEPTH INVESTIGATION OF THE FIRST CB2R-TARGETED ALLOSTERIC MODULATOR: FROM METABOLOMICS AND PROTEOMICS TO RADIOTRACER DEVELOPMENT FOR TUMOR IMAGING

Ferrisi R., Baron G., Altomare A., Maspero M., Scarpa E., Cazzaniga A., Rizzello L., Gado F., Manera C., Coliva A., Aldini G., Moresco R.M., Dallanocce C.110

P040 - 5-HTR_{1A} ANTAGONIST FOR TARGETING IN PROSTATE CANCER CELLS

Fiorino F., Ambrosio M.R., Caliendo G., Corvino A., Formisano P., Magli E., Andreozzi G.111

P041 - IDENTIFICATION OF NATURAL HDAC8 INHIBITORS THROUGH SHAPE VIRTUAL SCREENING AND IN VITRO VALIDATION: UNVEILING THE APOPTOTIC ANTICANCER MECHANISM

Gargano A., González Bakker A., Rocca R., Maggisano V., Puerta A., Bulotta S., Padrón J.M., Alcaro S.112

P042 - NEW ANTICANCER AGENTS FROM A BERBERINE-BASED STRUCTURAL SIMPLIFICATION APPROACH

Giammarino F.M.P.R., De Vita S., Lauro G., Bifulco G., Ramunno A.113

P043 - MECHANISTIC INVESTIGATION AND TARGET VALIDATION OF BITHIAZOLE DERIVATIVES AS α -SARCOGLYCAN CORRECTORS

Ribaud G., Anyanwu M., Giannangeli M., Carotti M., Sandonà D., Gianoncelli A.114

P044 - TARGETED DEGRADATION OF THE ZEB1-ALDH1A3 AXIS IN CANCER USING PROTACS AND OLIGONUCLEOTIDE-BASED PROTACS

Gioiello L., Lesca G., Ferrara G., Fiorino A., Di Martino R.M.C., Garavaglia S., Fallarini S., Galli U., Pinton G., Sangaletti S., Pirali T.115

P045 - IN SILICO EVALUATION OF BIOACTIVE CONSTITUENTS FROM A FUNCTIONAL BEVERAGE TARGETING HUMAN PANCREATIC LIPASE

Greco I., Rocca R., Alcaro S.116

P046 - SYNTHESIS AND BIOLOGICAL EVALUATION OF UROLITHIN A DERIVATIVES

Iacopetta D., Improta L., Scarcelli E., Ceramella J., Aiello F., Ramunno A., Giammarino F.M.P.R., Catalano A., Sinicropi M.S.117

P047 - FIRST-IN-CLASS X-RAY-ACTIVATABLE PARP_i PRODRUGS FOR SPATIOTEMPORAL CONTROL OF PARP1 INHIBITION IN SOLID TUMORS: DESIGN AND IN SILICO EVALUATION

La Monica G., Bono A., Alamia F., Tocco D., Lauria A., Martorana A.118

P048 - UNLOCKING THE UNDRUGGABLE: COMPUTER-AIDED STRATEGIES FOR TARGETING RHOA

La Serra M.A., Vidossich P., De Vivo M.119

P049 - TARGETING MAGL THROUGH REVERSIBLE INHIBITION: EXPANSION OF A PIPERIDINE-BASED CHEMICAL SPACE

Landucci E., Tuccinardi T., Bertini S., Granchi C., Macchia M.120

P050 - DESIGN OF NEW REVERSIBLE MAGL INHIBITORS VIA BIOISOSTERIC REPLACEMENT OF THE PIPERAZINE CORE

Lonzi C., Bononi G., Ciccone L., Macchia M., Tuccinardi T., Minutolo F., Granchi C.121



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P051 - SYNTHESIS AND PRELIMINARY EVALUATION OF AKR INHIBITORS AS PROSPECTIVE AGENTS FOR THE MANAGEMENT OF CANCER AND DIABETES MELLITUS COMPLICATIONS	
Maccari R., Avannatti M., Balestri F., Del Corso A.	122
P052 - RATIONAL DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF N-[(3,5-DIMETHYLPHENYL)METHYL]-1H-BENZIMIDAZOLE DERIVATIVES AS PORCINE PANCREATIC ELASTASE INHIBITORS	
Mancuso F., Pitasi G., Floris S., Fais A., De Luca L., Gitto R.	123
P053 - MOLECULAR DYNAMICS-GUIDED STRUCTURE-BASED VIRTUAL SCREENING REVEALS NOVEL CANDIDATE LIGANDS TARGETING THE WEST NILE VIRUS RNA G-QUADRUPLEX	
Curcio A., Russo A., Quiros-Roldan E., Alcaro S., Rocca R., Artese A.	124
P054 - LIGHT-MODULABLE DUAL AChE/MAO-B INHIBITION VIA AURONE-BASED MOLECULAR PHOTOSWITCHES	
Manenti G., Cabral S.M.E., de Candia M., Deruvo C., Brizzi A., Mugnaini C., Corelli F., Cappelli A., Altomare C.D., Paolino M.	125
P055 - DISCOVERY OF A NOVEL WATER-SOLUBLE PRODRUG OF MEDS433: IMPROVING SOLUBILITY AND BIOAVAILABILITY OF A POTENT hDHODH INHIBITOR FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA	
Mannella I., Sainas S., Circosta P., Giorgis M., Lolli M.L., Boschi D.	126
P056 - ARTIFICIAL INTELLIGENCE-GUIDED REPURPOSING REVEALS A SMOOTHENED- AND SIRT1-DEPENDENT MECHANISM BEHIND THE PROMYELINATING ACTIVITY OF LAQUINIMOD	
Dominicis A., D'Amore V.M., Recchia A.D., Di Leva F.S., Santoro F., Fabiano T., Arosio D., Seneci P., Ragnini-Wilson A., Marinelli L.	127
P057 - NUTRACEUTICAL POTENTIAL OF ANCIENT WHEATS: EXPLORING THEIR DISTINCTIVE BIOLOGICAL PROPERTIES	
Scarcelli E., Marra M., Iacopetta D., Ceramella J., Sicari V., Gattuso A., Aiello F., Sinicropi M.S.	128
P058 - DESIGN, SYNTHESIS AND PRELIMINARY EVALUATION OF NEW CATHEPSIN L INHIBITORS AS POTENTIAL ANTITUMOR AGENTS	
Martorano L.P., Ciaglia T., Vestuto V., Musella S., Di Sarno V., Smaldone G., Di Matteo F., Napolitano V., Lauro G., Ostacolo C., Bertamino A.	129
P059 - DEVELOPMENT OF GY915, A DUAL KINASE/HDAC INHIBITOR WITH IN VIVO EFFICACY	
Giacomello M., Verona M., Vaccarin C., Chilin A., Marzaro G.	130
P060 - DECODING MYCOBACTERIAL SALICYLATE SYNTHASES: STRUCTURAL CLUES FOR NEW DRUGS	
Meneghetti F., Mori M., Tresoldi A., Villa S., Stelitano G., Chiarelli L.R., Bellinzoni M., Covacevich S., Cassetta A.	131
P061 - SANGIOVESE GRAPE SEEDS EXTRACT AS A NUTRACEUTICAL CANDIDATE FOR THE SUPPORT OF CARDIAC AMYLOIDOSIS THERAPY	
Mirabeni M., Ciccone L., Zizzi F., Terolli M., D'Onofrio C., Bramanti E., Campanella B., Bertini S., Nencetti S., Macchia M.	132
P062 - SYNTHESIS OF NOVEL 3-PHENOXYPROPAN-2-OL DERIVATIVES AS POTENT AZOLE-BASED HEME OXYGENASE 1 INHIBITORS	
Mocka S., Modica M.N., Contarino G., Distefano F., Pittalà V., Salerno L., Romeo G., Consoli V., Buttice A., Miggiano R., Siracusa L., Intagliata S.	133
P063 - QUERCETIN ATTENUATES THERMAL BURN-INDUCED INFLAMMATION BY MODULATING PRO-INFLAMMATORY MEDIATORS AND COX/NOS EXPRESSIONS IN RATS	
Al-Roujayee A.S., Ahmed M.M., Mohany M.	134
P064 - INVESTIGATION OF C(sp²)-C(sp³) NAPHTHOCOUMARIN ATROPISOMERS FOR THE TREATMENT OF ENTEROVIRUS EV-A71 INFECTIONS	
Moi D., Cabua M.C., Viridis L., Sanna G., Secci F.	135
P065 - THE PyRMD STUDIO ADVANCEMENT: AN ACCESSIBLE AI-POWERED PLATFORM FOR ULTRA-LARGE VIRTUAL SCREENING	
Natale B., Waqas M., Roggia M., Di Maro S., Cosconati S.	136



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica**P066 - DEVELOPMENT OF PHOTOSWITCHABLE LIGANDS FOR THE MODULATION OF THE GPR120 RECEPTOR**

Noli C., Brizzi A., Mugnaini C., Corelli F., Pessina F., Paolino M.137

P067 - SYNTHESIS AND FUNCTIONALIZATION OF PYRAZOLO[3,4-d]PYRIMIDINE DERIVATIVES AS POTENTIAL Src KINASE INHIBITORS

Oleari F., Schenone S., Grossi G., Musumeci F., Carbone A.138

P068 - SUSTAINABLE SYNTHESIS AND BIOLOGICAL EVALUATION OF TACRINE-LIKE MULTI-TARGET HYBRIDS AS ANTI-ALZHEIMER CANDIDATES

Cerini M., Paparella M., Leuci R., Roselli V., Loiodice F., Laghezza A., Tortorella P., Piemontese L.139

P069 - NADES-BASED GREEN EXTRACTION OF GRAPE POMACE POLYPHENOLS: A SUSTAINABLE APPROACH TO NOVEL DIETARY SUPPLEMENTS

Roselli V., Leuci R., Paparella M., Pugliese G., Luz C., Moreno A., Manyes L., Tarricone L., Laghezza A., Tufarelli V., Gambacorta L., Meca G., Piemontese L.140

P070 - MAPPING THE CONFORMATIONAL LANDSCAPE OF HuR: AN IN SILICO STUDY ON THE IMPACT OF PHOSPHORYLATION SITES

Paravati M.R., Marchese E., Ambrosio F.A., Castoria G., Tesei A., Costa G., Collina S., Alcaro S.141

P071 - PHARMACOKINETIC CHARACTERIZATION THROUGH INTEGRATED DMPK/PK APPROACHES FOR ANTI-INFLAMMATORY MOLECULES

Pellecchia S., Pepe G., Basilicata M., Aquino G., Ostacolo C., Manfra M., Campiglia P., Bertamino A.142

P072 - COMPUTATIONAL DESIGN AND SYNTHESIS OF CANDIDATE DUAL INHIBITORS TARGETING ADAM17 AND KRas-G12C AGAINST NSCLC

Pinzi L., Crispino E., Rossello A., Nuti E., Rastelli G.143

P073 - IDENTIFICATION OF CHLORMIDAZOLE AS A REPURPOSING CANDIDATE AGAINST AGGRESSIVE PROSTATE CANCER THROUGH CHEMOINFORMATICS AND MACHINE LEARNING

Pinzi L., Bernal L., Martinelli T., Rinaldi A., Piccinini I., Belluti S., Bisi N., Imbriano C., Rastelli G.144

P074 - NOVEL α -GLUCOSIDASE INHIBITORS BASED ON BENZIMIDAZOLE CORE STRUCTURE: FROM SYNTHESIS TO COMPUTATIONAL STUDIES

Pitasi G., Mancuso F., Floris S., Ielo L., Fais A., Gitto R., De Luca L.145

P075 - THE SUBSTRATE REDUCTION APPROACH FOR THE TREATMENT OF GAUCHER DISEASE: DESIGN AND DEVELOPMENT OF NOVEL GLUCOSYLKERAMIDE SYNTHASE INHIBITORS

Prencipe F., Brancale A., Bufano M., Pavan E., Carosati E., Spalluto G., Federico S., Da Ros T.146

P076 - MULTITARGET-DIRECTED LIGANDS TARGETING VIRAL PROTEASES AND HUMAN CATHEPSIN L AGAINST SARS-COV-2

Previti S., Maccari R., Ettari R., Kuzikov M., Schirmeister T., Zappalà M.147

P077 - DEVELOPMENT OF SELECTIVE HUMAN CATHEPSIN L INHIBITORS WITH ANTI-GLIOBLASTOMA PROPERTIES

Previti S., Calcaterra E., De La Pradilla Ibáñez A.F., Maus H., Cigala R., Labellarte D., Ettari R., Esposito E., Schirmeister T., González F.V., Zappalà M.148

P078 - PIN1 INHIBITION BY atRA-INSPIRED ANALOGUES: AN INTEGRATED AND MINIATURISED ANALYTICAL APPROACH FOR STABILITY PROFILING IN ANTICANCER DRUG DISCOVERY

Protti M., Noreen S., Iattoni C.P., Snider M.F., Di Lecce R., Mandrioli R., Giorgis M., Vitale R.M., Del Sal G., Lolli M.L., Pippione A.C., Mercolini L.149

P079 - MULTIVALENT PIPERIDINE-BASED β -GLUCOSIDASE INHIBITORS FOR OVERCOMING CHEMORESISTANCE IN BREAST CANCER THERAPY

Milano F., Nito A., Buco F., Quarta E., Matassini C., Cardona F., Gaballo A., Goti A., Quarta A., Marradi M., Ragusa A.150



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P080 - IDENTIFICATION OF NEW ANTIMICROBIAL COMPOUNDS IN ENVIRONMENTAL BACTERIA: A MULTIDISCIPLINARY APPROACH AGAINST RESISTANT PATHOGENS	
Espina L., Lucía A., Delpozzo F., Negredo L., Anyanwu M., Romanello M.B., Rosa S., Gianoncelli A., Ribaud G.	151
P081 - UNLOCKING THE ORPHAN RECEPTOR GPR183: AI-DRIVEN DISCOVERY OF NOVEL LIGANDS	
Roggia M., Andersson L., Kozielowicz P., Cosconati S.	152
P082 - DESIGN, SYNTHESIS, AND CHARACTERIZATION OF LTR III-BINDING BIOISOSTERES CONJUGATED WITH NAPHTHALENE DIIMIDES FOR DUAL HIV-1 INHIBITION	
Rotundo G., Cannistrà M.F.S., Rocca R., Doria F., Gargano A., Xiao W.J., Alcaro S.	153
P083 - TWO-PRONGED PHENOTYPIC APPROACH TO IDENTIFY NEW AND PROMISING ANTI-MYCOBACTERIUM ABSCESSUS AGENTS	
Dragone C., Poma N., Massari S., Manfroni G., Barreca M.L., Rindi L., Sabatini S.	154
P084 - MICROWAVE-ASSISTED SYNTHESIS OF TUBULIN ASSEMBLY INHIBITORS AS ANTICANCER AGENTS	
Santelli M., Masci D., Puxeddu M., Hamel E., Silvestri R., La Regina G.	155
P085 - DISCOVERY OF NOVEL INDOLE-BASED DERIVATIVES AS POTENT SARS-COV-2 INHIBITORS TARGETING THE SPIKE PROTEIN	
Sardo I., Bertamino A., Ostacolo C., Franci G., Campiglia P.	156
P086 - NOVEL <i>para</i>-PHENYLENEDIAMINE-BASED DERIVATIVES AS RECEPTOR TYROSINE KINASE-LIKE ORPHAN RECEPTOR 1 (ROR1) INHIBITORS: AN IN VITRO PRELIMINARY CHARACTERIZATION	
Smaldone G., Miranda M.R., Di Matteo F., Napolitano V., Aliberti M., Musella S., Di Sarno V., Lauro G., Bifulco G., Pepe G., Aquino G., Tecce M.F., Gomez-Monterrey I.M., Campiglia P., Ostacolo C., Bertamino A., Vestuto V., Ciaglia T.	157
P087 - PHENOTYPE-GUIDED TARGETING OF THE ADENOSINE AXIS: SUBTYPE-SPECIFIC TUMOR CONTEXT MODULATORS FROM 3D MODELS	
Smirnov A., Francucci B., Spinaci A., Buccioni M., Dal Ben D., Lambertucci C., Volpini R., Marucci G.	158
P088 - ISOCYANIDES: AN UNCONVENTIONAL FUNCTIONAL GROUP AS A HEME-COORDINATING MOTIF FOR IDO1 INHIBITION	
Sosta R., Buttice A., Mazzoni D., Tron G.C., Di Martino R.M.C., Fallarini S., Pirali T.	159
P089 - TARGETING TLR-MEDIATED INFLAMMATION IN METABOLIC AND SYSTEMIC DISEASE	
Spinelli L., Lauber F., Vittorio S., Vistoli G., Weindl G., Fumagalli L.	160
P090 - DEVELOPMENT OF NOVEL ORTHOSTERIC NS2B/NS3 PROTEASE INHIBITORS	
Starvaggi J., Esposito F., Tramontano E., Gütschow M., Ettari R.	161
P091 - DEVELOPMENT OF NOVEL ALLOSTERIC GLUTAMINASE 1 INHIBITORS AS ANTICANCER AGENTS	
Vezzoli M., Francesconi V., Poggialini F., Vagaggini C., Schenone S., Dreassi E., Fossa P., D'Ursi P., Tonelli M., Carbone A.	162
P092 - DISCOVERY OF NOVEL SALICYLATE SYNTHASE INHIBITORS AS ANTI-VIRULENCE AGENTS AGAINST MYCOBACTERIUM ABSCESSUS	
Villa S., Mori M., Tresoldi A., Stelitano G., Chiarelli L.R., Bellinzoni M., Covaceutzach S., Cassetta A., Meneghetti F.	163
P093 - METABOLEX: AN INTEGRATED PLATFORM FOR METABOLITES GENERATION AND METABOLIC PATHWAY ANALYSIS	
Vittorio S., Lunghini F., Agazzi G., Tazzari V., Fava A., Macorano A., Vistoli G., Beccari A.R.	164
P094 - Nav1.5 N347K REMODELS THE ELECTROSTATIC LANDSCAPE FOR MEXILETINE BINDING: MOLECULAR DYNAMICS INSIGHTS INTO BRUGADA SYNDROME	
Yesilyurt Y., Multari S., Papetti D.M., Nobile M.S., Besozzi D., Peri F., Rivolta I.	165
P095 - MEGA PROTAC RELOADED: A ROUTE TO TERNARY COMPLEX MODELING LEVERAGING KNOWLEDGE-BASED BURIED-SURFACE AREA AND LINKER CONFORMATIONAL FREEDOM DATA	
Zambra M., Panagiotis K.D., Sandrone G., Vergani B., Marchini M., Riedl R., Gazzola S.	166



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



P096 - NOVEL ANTITUSSIVE DERIVATIVES AS POTENTIAL SIGMA RECEPTOR LIGANDS

Zampieri D., Scorzato T., Cartosati E., Nzanguim C.T.N., Salvi S.167

P097 - DEVELOPMENT OF NITROGEN-BASED COMPOUNDS AS ANTIVIRAL AGENTS AGAINST FLAVIVIRUSES

Zarbo L., Albano A., Cara E., Ruggieri G., Patacchini E., Madia V.N., Saccoliti F., Messori A., Marcorelli B., Loregian A., Costi R., Di Santo R.168

P098 - MOLECULAR STRIPTEASE OF A THIADIAZOLOPYRIMIDINE HIT YIELDS A STREAMLINED, ARTEFACT-FREE NADPH MIMIC FOR NOX INHIBITION

Fabbri E., Mancini A., Lambona C., Macrì S., Nalli M., Quilli F., Pandolfi F., Raimondo D., Marchese S., Mattevi A., Lee J., Choi M., Bae Y.S., Hristova-Avakumova N., Kondeva-Burdina M., Stefanova D., Anastassova N., Valente S., Rotili D., Mai A.169

P099 - SIMPLIFICATION AND DERIVATIZATION OF QUINOLINE-CONTAINING M41 LEAD TO THE DISCOVERY OF NADPH OXIDASE ISOFORM-SELECTIVE INHIBITORS EFFECTIVE IN CANCER CELLS

Lambona C., Marchese S., Noce B., Massari M., Ciampoli D., Fiorentino F., Zwergel C., Fabbri E., Mancini A., Quilli F., Pandolfi F., Raucchi A., Fioravanti R., Corinti D., Re M., Mormino A., Garofalo S., Limatola C., Mele D., Capasso L., Casalino R., Nebbioso A., Altucci L., Raimondo D., Mattevi A., Mai A., Valente S.170

P100 - DEVELOPMENT OF NOVEL SRPIN340-INSPIRED 1,2,3-TRIAZOLE DERIVATIVES: SYNTHESIS, CHARACTERIZATION AND ANTITUMOR EVALUATION

Aniceto D., Santiago S.S., Azevedo G.T., Rocha G.G., Lima P.M.A.P., Costa A.V., Araújo T.G., Teixeira R.R.171

P101 - SYNTHESIS AND EVALUATION OF THE ANTIMELANOMA ACTIVITY OF 3,4,5-TRIMETHOXYCINNAMIC ACID-BASED 1,2,3-TRIAZOLE DERIVATIVES

Santiago S., Aniceto D., Teixeira R.R., Herédia A.O., Costa A.V., Barbosa L.A.S., Araújo T.G.172

P102 - COMPUTATIONAL DRUG REPURPOSING THROUGH HOMOLGY MODELING OF MUTATED VARIANTS OF LANOSTEROL 14 α -DEMETHYLASE

Ofria L., Giosa D., D'Alì M., Giuffrè L., Genovese F., Romeo O., Iraci N.173



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



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PLENARY LECTURES



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

PL01

THE GOLDEN AGE OF PEPTIDES: EMERGING CHALLENGES AND FUTURE OPPORTUNITIES

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Peptide synthesis remains one of the most dynamic and innovative areas of modern chemistry, driven by the growing importance of peptide-based therapeutics across a wide range of disease areas. Despite continuous advances in synthetic methodologies and process technologies, the synthesis of peptides has changed surprisingly little over the past three decades. The overwhelming majority of peptides, whether synthesized for research purposes or commercial applications, are still produced using solid-phase peptide synthesis (SPPS) based on the Fmoc/tBu protection strategy. This well-established platform typically relies on highly swellable gel-type resins, large volumes of polar aprotic solvents such as DMF and DCM, carbodiimide-based coupling systems, and TFA-containing cocktails for final deprotection and cleavage. Today, however, the peptide manufacturing landscape is undergoing a profound transformation. This change is being driven by the emergence of two distinct but equally demanding classes of peptide therapeutics. The first includes GLP-1 receptor agonists and related metabolic peptides, which are often composed of more than thirty amino acids and incorporate lipidated structures to enhance pharmacokinetic performance. The extraordinary clinical and commercial success of these molecules has created an unprecedented need for manufacturing at kilogram, multi-kilogram, and even ton scales, placing immense pressure on existing production technologies. The second class comprises highly engineered medium-sized peptides, typically containing around 10–20 amino acids, but characterized by complex architectures including mono- and polycyclic structures, multiple disulfide bridges, and a high proportion of non-proteinogenic amino acids. These molecules frequently challenge the limits of conventional SPPS, requiring enhanced coupling efficiency, improved control of side reactions, and innovative approaches to purification and process development. Together, these trends are forcing the peptide community to reconsider long-standing synthetic paradigms. Beyond the need for greater productivity and scalability, there is increasing recognition that future manufacturing processes must also address environmental sustainability, solvent consumption, waste generation, and the elimination of polyfluorinated chemicals. In this presentation, we will discuss recent developments from our laboratory aimed at enabling a new generation of peptide manufacturing technologies. Particular emphasis will be placed on the design of rigid polymeric supports that dramatically reduce solvent requirements during synthesis, as well as swellable macroporous resins that enable the use of greener and more readily recyclable solvents. We will present advances in coupling chemistry, including novel activating reagents that combine high reaction efficiency with reduced epimerization and the formation of easily removable byproducts. Alternative deprotection strategies based on non-polyfluoroalkylated acids will also be described as potential replacements for conventional TFA-based processes. Finally, we will explore emerging liquid-phase peptide synthesis (LPPS) approaches that exploit innovative molecular tags and separation technologies to combine the operational simplicity of solution-phase chemistry with the efficiency traditionally associated with SPPS. These developments illustrate how the field is evolving toward more sustainable, economically viable, and scalable manufacturing solutions capable of meeting the growing demands of next-generation peptide therapeutics.



XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



PL02

ARTIFICIAL INTELLIGENCE POWERED PLATFORMS FOR DRUG DISCOVERY

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Higher quality, accelerated timelines and cost reduction are imperatives for drug discovery today and essential to bring better drugs to patients faster.

Foundation models, protein structure prediction and co-folding enhance biological understanding and improve the identification of chemical starting points. Generative AI for molecular design, synthesis prediction and predictive model platforms accelerate hit and lead optimization.

Agentic AI supports scientists with improved decision making in drug discovery projects.

Integrated application of all these innovations will reduce timelines and costs per project as well as numbers of compounds to be made and tested. Lab automation enhances advanced design-make-test-analyze workflows, accelerates compound profiling and ensures standardized test conditions and proper data integration. Combination of lab automation with digital twins may in the future enable closed loop drug discovery based on self-driving labs.

This presentation summarizes how AI-powered innovations are currently combined with the aim to bring better drugs to patients faster.



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PL03

PROGRAMMING DISEASE BIOLOGY WITH CHEMISTRY: DESIGNING MOLECULES, DESIGNING MECHANISMS

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For decades, medicinal chemistry has focused on designing molecules that bind biological targets with high potency and selectivity. Today, the discipline is evolving beyond target engagement towards the rational design of molecular mechanism that control protein function, cellular networks and ultimately disease biology.

This talk will illustrate how chemically induced proximity is driving this transformation, drawing lessons from the clinical progress of **ER-targeting PROTACs and degraders** [1], **molecular glue degraders** and **Cyclophilin-mediated RAS inhibitors**, and **MTA-cooperative PRMT5 inhibitors** [2]. Together, these examples show how small molecules can induce, stabilise or disrupt protein interactions to create entirely new therapeutic mechanisms. Emerging programmable proximity-induced proximity-based systems further illustrate how chemistry can exploit or engineer biological context to expand the therapeutic landscape.

These advances have been enabled by innovations in medicinal chemistry that extend beyond traditional "rule-of-five" principles. Three-dimensional molecular design, conformational control [3] and deeper understanding of protein dynamics [4] are enabling increasingly complex molecules to achieve oral bioavailability, tissue penetration and clinical efficacy.

Together, these advances illustrate the evolution of medicinal chemistry – from designing molecules that bind targets, to designing mechanisms that modulate disease biology, and ultimately to programming disease biology with chemistry. This merging paradigm is redefining how new medicines are discovered and expanding the opportunities for future therapeutic innovation.

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National Meeting on
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Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



PL04

FROM PATHWAYS TO PATIENTS: METABOLOMICS IN MODERN DRUG DISCOVERY

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The increasing complexity of human diseases demands new strategies capable of connecting molecular phenotypes with actionable therapeutic mechanisms. In this context, metabolomics has evolved from a descriptive analytical discipline into a powerful discovery platform that contributes to medicinal chemistry through mechanistic target identification, pathway elucidation, and evaluation of drug response. By capturing the downstream functional state of biological systems, metabolomics provides a direct window into biochemical alterations associated with disease progression, therapeutic intervention, and host-pathogen interactions.

Particularly, untargeted metabolomics approaches have demonstrated an exceptional capacity to generate unbiased hypotheses and reveal unexpected biological mechanisms. Beyond biomarker discovery, global metabolic profiling enables the identification of dysregulated pathways, metabolic vulnerabilities, and signalling networks that may constitute novel therapeutic targets. Furthermore, the integration of metabolomics with systems biology and pharmacology is facilitating a deeper understanding of mechanisms of action and resistance processes relevant to drug development.

This lecture will present recent examples illustrating the role of metabolomics and lipidomics in mechanism-oriented biomedical research. Special attention will be devoted to the application of untargeted approaches for pathway elucidation in infectious diseases and host-directed therapeutic strategies. In particular, recent lipidomics studies in mucormycosis revealed profound alterations in host lipid metabolism characterized by decreased free fatty acids and increased oxylipin production, uncovering inflammatory lipid mediator networks potentially involved in disease pathogenesis and therapeutic modulation. These findings exemplify how metabolomics-driven approaches can identify biologically relevant pathways with direct implications for medicinal chemistry and translational drug discovery.

Overall, this presentation will discuss the transition of metabolomics from biomarker-oriented studies toward a central role in therapeutic hypothesis generation, mechanistic pharmacology, and target discovery in modern medicinal chemistry.



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17th Young Medicinal Chemists' Symposium
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KEYNOTE LECTURES

KN01

TUBULIN TARGETING DRIVES FERROPTOSIS IN CANCER

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Ferroptosis, an iron-dependent form of regulated cell death, has emerged as a promising strategy to overcome apoptosis resistance in cancer [1]. As part of our continuing effort to develop pyrrole-based tubulin assembly inhibitors, we progressed from 3-aryl-1-arylpyrroles and 3-aryl-1,4-diarylpyrroles to 3-aryl-1-aryl-4-heterocyclic pyrroles, and finally to 3-aryl-diheterocyclic pyrroles (ARDHEPs), compounds that bind to the colchicine site and inhibit tubulin polymerisation [2–10]. Here, we show that tubulin targeting can drive ferroptosis across distinct tumour types (**Figure 1**).

ARDHEP **1** exhibited potent antiproliferative activity in glioblastoma and ovarian cancer cells, whereas ARDHEP **2** was highly active in triple-negative breast and colorectal cancer cells, including efficacy in an HCT116 xenograft [6,9]. Both compounds retained strong inhibition of tubulin polymerisation and colchicine binding, supporting tubulin as the primary target [6,9].

Their antitumour effects were consistently associated with ferroptotic features, including oxidative stress, iron-dependent lipid damage, modulation of ferroptosis-related genes, altered redox homeostasis, mitochondrial abnormalities, and downregulation of GPX4, ferritin-related pathways, Ki67, and CD31 [6,9]. Overall, these findings support a unifying model in which colchicine-site tubulin inhibition perturbs iron homeostasis and redox balance, thereby promoting ferroptotic cell death in multiple aggressive and therapy-resistant cancers.

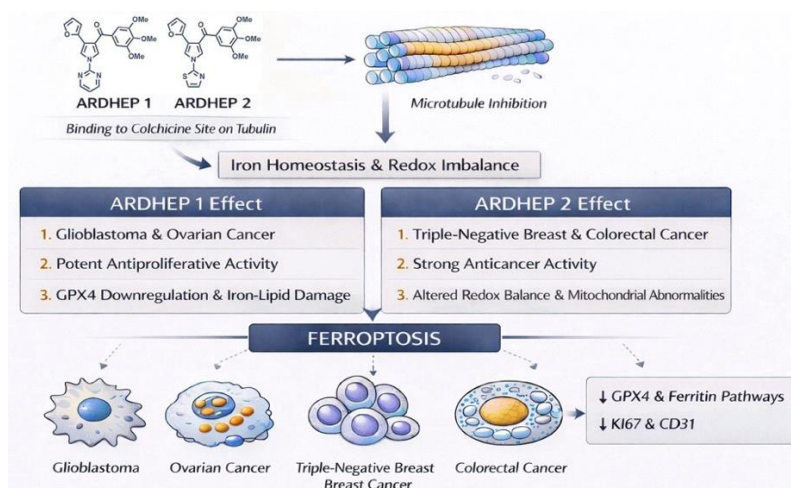


Figure 1. Inhibition of Tubulin Polymerisation Promotes Ferroptosis in Cancer.

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17th Young Medicinal Chemists' Symposium
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KN02

ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY: READING THE SMALL PRINT

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Artificial Intelligence (AI) is rapidly transforming drug discovery, enabling unprecedented advances in virtual screening, molecular design, and predictive modeling [1]. However, the widespread adoption of AI-based approaches is often accompanied by a limited understanding of their underlying assumptions and limitations.

In this lecture, we will explore the “small print” of AI in medicinal chemistry, focusing on key challenges related to data quality, model generalization, and, most critically, the definition of the applicability domain. Particular emphasis will be placed on the gap between perceived and actual model reliability, highlighting how predictions are often used without assessing whether they are trustworthy.

Building on recent findings, we will show that model reliability is inherently context-dependent and prediction-specific, and that no single strategy can universally define when predictions can be considered valid [2]. Through selected case studies and the presentation of a novel approach for applicability domain assessment, we will discuss how more robust and transparent use of AI models can be achieved.

The goal of this lecture is to move beyond both excessive skepticism and uncritical enthusiasm, providing a balanced and practical perspective on the appropriate use of AI models in medicinal chemistry.

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National Meeting on
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Messina, Italy - September 13-16, 2026



17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



KN03

TARGETING COPPER METABOLISM IN CANCER FOR THERANOSTICS: FROM COPPER(I)-BASED SMALL MOLECULES TO SELF-ASSEMBLED SUPRAMOLECULAR NANOPLATFORMS

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Cancer has increasingly been described as a form of “cuproplasia”, reflecting the elevated copper levels observed in many tumors and the key role of copper in pathways involved in cell proliferation and invasion [1]. This difference between normal and cancer cells represents a selective target for copper-based therapeutics. We developed several classes of copper complexes, with particular emphasis on Cu(I) phosphino derivatives, which exhibit remarkable antiproliferative activity and selectivity [2-4].

Taking advantage of the applicability of copper radioisotopes in the medicinal field, we explored the theranostic potential of some new Cu(I) complexes by radiolabeling them with ⁶⁴Cu and ⁶⁷Cu. PET/CT imaging and biodistribution studies in human xenograft models highlighted the importance of ligand hydrophilic balance and complex stability for tumor-selective accumulation.

To further improve tumor targeting and therapeutic performance, we have recently developed innovative copper-conjugated self-assembling nanosystems to enhance tumor accumulation and efficacy. These supramolecular nanoplatforms show strong translational potential for next-generation theranostic applications.

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National Meeting on
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Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

KN04

MINIATURIZED SAMPLE PREPARATION TO DRIVE INNOVATION IN PHARMACEUTICAL ANALYSIS

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Modern pharmaceutical analysis is increasingly expected to be greener, faster and more cost-effective, while preserving, and often improving, the analytical reliability required across medicinal chemistry, drug discovery and drug development, as well as downstream bioanalytical applications such as therapeutic drug monitoring (TDM), pharmacokinetics, pharmacodynamics and forensic investigation. Miniaturized sample preparation is a central enabler of this evolution, reducing solvent, reagent and matrix consumption, while supporting higher throughput, enhanced selectivity and efficient analyte extraction. These benefits are particularly relevant in early-stage research, where sample availability is often limiting and where fast turnaround directly impacts decision-making. To be truly effective, sampling, sample treatment and instrumental analysis must be jointly developed, optimized and validated as a single fit-for-purpose workflow, with analytical performance considered from the earliest stages of method design rather than as a downstream concern [1].

The field is rapidly moving beyond first-generation miniaturization approaches toward volumetrically reliable, matrix-tolerant and highly reproducible techniques. Advanced microsampling now relies on absorptive formats, capillary-based devices and microfluidic platforms generating defined-volume specimens, addressing pre-analytical variability that becomes critical at low sample volumes (from uncertainty in effective sampled volume to density- and viscosity-related biases, including hematocrit effects) [2]. Such platforms also offer improved analyte stability and simplified logistics, which are particularly valuable in decentralized or longitudinal study designs. Miniaturized pretreatment strategies, such as micro-solid-phase extraction (micro-SPE) and stop-and-go extraction (StAGE), complement these formats, enabling selective isolation and pre-concentration from very small volumes while remaining fully compatible with chromatographic and mass spectrometric analysis, and lending themselves to parallelization for medium- to high-throughput contexts.

Across drug discovery and development studies, preclinical and clinical PK/PD, TDM and forensics, these approaches have demonstrated reliability, data reproducibility, analyte stability assurance and ease of application, often with a clear advantage in terms of sustainability and cost per sample.

Looking ahead, automation is making miniaturized sample treatment more repeatable and less operator-dependent [3], while 3D printing is enabling rapid, customized fabrication of sampling and extraction devices. Together, these developments outline a clear trajectory toward a greener, leaner and reliable pharmaceutical analysis future, increasingly oriented toward the individual subject, with patient-centric strategies and the expansion of decentralized and point-of-care testing paradigms.

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KN05

THE FASCINATING STORY OF N-ADAMANTYL ANTHRANILAMIDE DERIVATIVES: DESIGN AND DEVELOPMENT OF SELECTIVE CB2R LIGANDS

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Cannabinoid receptor 2 (CB2R), a G_i protein-coupled receptor of the endocannabinoid system, is predominantly expressed in immune tissues and is upregulated in microglial cells under pathological conditions, suggesting a relevant role in inflammatory and neurodegenerative disorders. In this context, a series of N-adamantyl anthranilamide derivatives was designed, synthesized, and evaluated for binding affinity and selectivity toward CB2R over CB1R. The molecular design was guided by the "three-arm pose" binding mode of the CB2R antagonist AM10257. Binding studies identified the highest affinity in compounds bearing either a phenyl group or hydrogen at arm 1 and a five-carbon alkyl chain at arm 2, while the carboxy-adamantyl amide moiety at arm 3 proved essential for receptor interaction. Selected derivatives showed marked selectivity for CB2R over CB1R and promising pharmacodynamic profiles. Molecular docking studies provided a rationale for the observed binding behaviour, while functional assays confirmed their potential as CB2R modulators [1]. Moreover, in vivo neuroprotection studies performed in a pharmacological mouse model of Alzheimer's disease induced by oligomerized Aβ_{25–35} peptide yielded encouraging results. To address the suboptimal pharmacokinetic profile of the previously selected derivatives, mainly associated with excessive lipophilicity, a systematic lead-optimization strategy was undertaken through the introduction of polar substituents around the anthranilamide scaffold. This approach enabled the identification of new selective CB2R ligands with improved pharmacokinetic properties. Their functional activity, anti-inflammatory effects, and activity on selected cell lines further support their potential therapeutic application in inflammatory and neurodegenerative diseases.

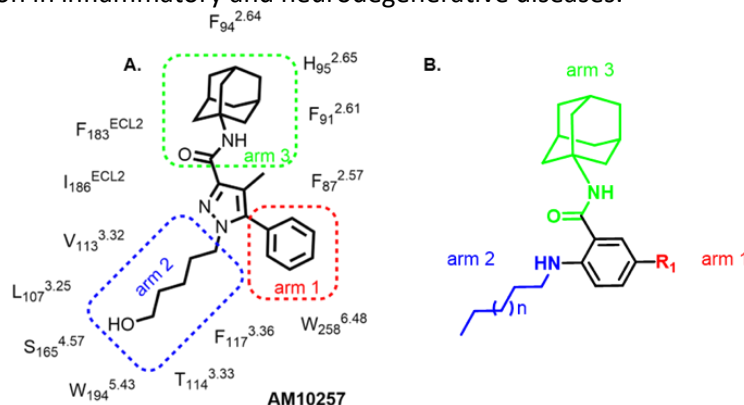


Figure 1: AM10257, CB2R antagonist (A), General structure of our N-adamantyl-anthranil amide derivatives (B).

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National Meeting on
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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica



KN06

A PRECISION MEDICINE FRAMEWORK FOR TARGETING DNA POLYMERASE ϵ IN COLORECTAL CANCER

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Precision medicine seeks to design patient-tailored therapeutic strategies by combining genomic, structural, and functional information within predictive frameworks. A major challenge is to translate omics-derived observations into mechanistic insight, explaining how patient-specific variants alter protein behavior and influence drug sensitivity. Here, we describe an integrated workflow that brings together genomics profiling, biochemical characterization, and structure-based computational analyses to identify clinically relevant mutations with actionable potential for drug discovery.

As a proof of concept, we focused on a colorectal cancer patient carrying a variant of unknown significance in POLE (DNA polymerase ϵ), a replication enzyme that functions in coordination with PCNA. Molecular dynamics simulations of the Pole:PCNA complex predict that this variant may disrupt functional motions and weaken communication between protein domains. These effects modify the relative arrangement of key catalytic subdomains and are predicted to impair DNA engagement. Consistent with these computational results, biochemical and biophysical experiments showed decreased DNA binding and reduced polymerase activity, confirming the functional impact of the variant.

By combining allosteric pathway analysis with pocket and epitope mapping, we identified a mutation-specific allosteric region suitable for ligand targeting. This site was then used to guide virtual screening of approved-drug libraries, followed by prioritization of candidate molecules according to predicted selectivity and experimental tractability. Overall, this pipeline led to the identification of mutation-selective effectors with experimentally validated activity and translational promise. More broadly, the study outlines a generalizable strategy for linking patient-specific gene variants to mechanism-driven therapeutic discovery.



KN07

FROM GPCR ACTIVATION TO LIGAND BINDING AND KINETICS: INTEGRATED COMPUTATIONAL APPROACHES FOR MEDICINAL CHEMISTRY

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G Protein-Coupled Receptors (GPCRs) are complex membrane proteins that regulate numerous physiological processes and serve as targets for nearly one-third of marketed drugs.¹⁻³ However, their pharmacological significance is governed by intricate processes — such as receptor activation and ligand binding — that occur on timescales requiring advanced computational strategies for accurate characterization. Here, we highlight the potential of free energy calculations powered by innovative machine learning-based algorithms in tackling fundamental medicinal chemistry challenges. Specifically, we first leveraged Path Collective Variables Metadynamics (PathCVs-MetaD) to elucidate the complete activation mechanism of the Adenosine A_{2A} receptor (A_{2A}R), identifying a novel pseudo-active receptor state and providing fresh insights into GPCR conformational dynamics and biased signaling.⁴ We then shifted our focus to ligand recognition, employing Funnel Metadynamics (FM) to reconstruct the full binding mechanism and the associated free energy landscape of selective and dual ligands targeting Formyl Peptide Receptors (FPRs),⁵⁻⁶ uncovering key determinants of FPR₁/FPR₂ selectivity. Additionally, by integrating Infrequent Metadynamics (In-MetaD) and Dynamic-Time-Warping, we characterized the kinetics of ligand binding and unbinding, capturing transition rates crucial for drug efficacy and development. Altogether, our findings not only deepen the understanding of GPCR function but also provide a robust framework for both fundamental research and drug discovery.

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KN08

COMPUTATIONAL CHALLENGES IN STRUCTURE-BASED DRUG DESIGN FOR RNA TARGETS

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Once viewed primarily as intermediates in the flow of genetic information, RNA molecules are now recognized as key functional components of cellular regulation. Their diverse biological roles make them attractive for the development of novel therapeutic strategies, such as RNA-modulating small-molecule drugs.[1] Computational approaches, including molecular dynamics (MD) simulations and molecular docking, are well-established in drug discovery against protein targets. However, their extension to RNA targets presents distinctive challenges,[2] largely due to the high flexibility and complex conformational dynamics of RNA structures.[3] In this context, MD simulations can be used to thoroughly explore the dynamical landscape of RNA molecules,[4] reveal features that govern RNA-ligand recognition[5] and provide mechanistic insights into the binding process.[6] Moreover, MD-derived conformational ensembles offer a practical route to incorporate RNA flexibility into molecular docking protocols in an ensemble-based fashion.[7] In this presentation, I will discuss our recent efforts to address these challenges through studies on selected RNA targets.

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KN09

**PROTEIN-DERIVED PEPTIDES TO TARGET G-QUADRUPLEX DNA:
FROM MOLECULAR RECOGNITION TO ANTICANCER ACTIVITY**

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DNA G-quadruplexes (G4s) are non-canonical nucleic acid structures involved in gene regulation, telomere maintenance, and other key biological processes [1,2]. Their formation and biological roles are tightly regulated by proteins that specifically recognize and interact with these structures [3]. As such, G4s represent highly attractive targets in medicinal chemistry [4]. However, achieving high selectivity with conventional small-molecule ligands remains a major challenge. Peptides derived from G4-binding proteins offer a promising alternative, combining sequence programmability with structural adaptability and extended interaction surfaces to achieve selective G4 recognition.

In this keynote, I will present our efforts toward the development of peptide-based G4 ligands, from molecular recognition to functional applications [5,6]. Inspired by natural G4-binding proteins, peptide sequences can be designed and subsequently optimized to better recognize, discriminate, and ultimately modulate G4 structures. Beyond binding, these peptide ligands can be engineered to improve key properties, including cellular uptake and ability to trigger biological effects. Furthermore, they can be functionalized with tailored warheads to form covalent interactions with their targets under spatiotemporal control [7].

Altogether, these studies establish peptide-based ligands as versatile and tunable tools for selective G4 recognition and modulation, offering new opportunities for the targeting of structurally diverse and dynamic DNA architectures, with potential therapeutic relevance.

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KN10

FROM SIGNALS TO KNOWLEDGE: MACHINE LEARNING IN ADVANCED DRUG ANALYSIS

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The growing complexity of pharmaceutical systems and the widespread use of high-dimensional analytical techniques have significantly increased the demand for advanced data analysis strategies. In this context, the transformation of raw instrumental signals into reliable chemical information represents a critical step in drug analysis, particularly when dealing with overlapping signals, unresolved components, and complex kinetic pathways [1].

Machine learning, within the broader framework of chemometrics, provides a robust set of data-driven approaches for addressing these challenges. The Multivariate Curve Resolution (MCR) approach enables the decomposition of complex datasets into chemically meaningful profiles, facilitating the identification of pure component spectra and their associated concentration profiles. The integration of machine learning algorithms further enhances pattern recognition, model robustness, and predictive capability across heterogeneous datasets, including multi-block and data fusion strategies that combine complementary information from different analytical platforms (e.g., LC-DAD-MS) [2].

These methodologies enable detailed characterization of drug stability, including the elucidation of degradation pathways and the reconstruction of kinetic profiles under stress conditions. Beyond stability studies, MCR-based approaches have been increasingly applied to pharmaceutical image analysis, enabling the resolution of chemical components in hyperspectral datasets, as well as in metabolomics, where they support the deconvolution and interpretation of complex biological matrices [3,4].

The combination of data-driven and mechanistic modeling supports a more comprehensive interpretation of pharmaceutical systems, improving both analytical performance and decision-making processes. Overall, the convergence of machine learning and chemometrics defines a data-centric paradigm in pharmaceutical analysis, enabling the extraction of useful knowledge from complex analytical signals and supporting the development of more predictive and reliable analytical workflows.

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National Meeting on
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ORAL COMMUNICATIONS

OC01

THE DISCOVERY OF THE FIRST IN CLASS THYMIDYLATE SYNTHASE DIMER DISRUPTERS FROM THE BINDING MODE AT THE DIMER INTERFACE TO IN VIVO STUDIES

Costi M.P.^a, Aiello D.^a, Ponterini G.^a, D'Arca D.^b, Marverti G.^b, Tagliazucchi L.^a, Moschella M.^a, Lamesta M.^b, Malpezzi G.^a, Venturelli A.^a, Remo G.^c, Pacifico S.^c, Pozzi C.^d

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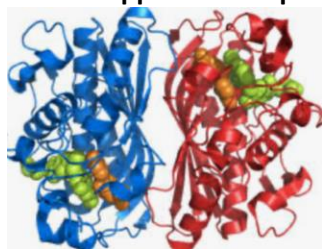
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Colorectal cancer (CRC) remains a leading cause of mortality, primarily due to intrinsic and acquired resistance to standard therapies. Driven by oncogene-induced replication stress, CRC cells rely heavily on nucleotide biosynthesis and replication stress response (RSR) signaling for survival. While classical inhibitors of thymidylate synthase (TS), the rate-limiting enzyme in de novo dTMP synthesis, are foundational to CRC treatment, their efficacy is constrained by dose-limiting toxicity and rapid resistance.

To overcome these challenges, we have developed a first-in-class series of allosteric TS inhibitors that disrupt TS homodimerization, a process essential for the enzyme's stability and activity [1]. Unlike active-site inhibitors such as 5-fluorouracil (5-FU), our lead compound, E7, promotes the proteasomal degradation of TS and avoids the compensatory upregulation of folate cycle proteins associated with drug resistance. By effectively collapsing the replication stress buffering capacity of tumor cells, this strategy offers a robust therapeutic alternative [2]. To prevent/delay treatment-induced resistance developed by classical TS inhibitors, we discovered the novel allosteric TS inhibitor **E7**. **E7** does not induce high expression of the folate cycle proteins, as 5FU, and downregulates TS by increasing its proteasomal degradation rate. **This novel inhibitor (dimer disrupters, (DDis), directed TS dimer disruption represents a mechanistically distinct approach compared with 5FU.**



In our recent work, we have confirmed that the compound class of benzothiophene derivatives shows a common mechanism of action with IC50 against HCT116 and HT29 CRC in the range of the 10-20 microMolar, showing a similar inhibition growth capacity in the same range. However, an important gap about the binding mode of the compound at the TS protein interface still exist. In this work, we elucidate the binding mechanism of these TS dimer disrupters at the protein interface through integrated molecular modeling and photoaffinity labeling (PAL) studies. Furthermore, we demonstrate that these compounds exhibit significant therapeutic efficacy in preclinical in vivo CRC models, providing a clear path toward overcoming the limitations of current clinical care.

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OC02

QUENCHING BACTERIAL COMMUNICATION: DISCOVERY AND PROFILING OF QUORUM SENSING INHIBITORS WITH ANTIBIOFILM AND ANTIVIRULENCE ACTIVITYLinciano P.^a, Milli G.^a, Menegussi Bellan E.^b, Pagano K.^c, Ragona L.^c, Pietrocola G.^b, Collina S.^a^a Department of Drug Sciences, University of Pavia, Viale Taramelli 12, Pavia, 27100, Italy^b Department of Molecular Medicine, Biochemistry Unit, University of Pavia, Viale Taramelli 3/b, Pavia, 27100, Italy^c Istituto di Scienze e Tecnologie Chimiche 'Giulio Natta', CNR, Milano, 20133, Italy
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Antivirulence strategies represent a promising adjunct or alternative to traditional antibiotic therapy, aiming to disarm pathogens by targeting virulence factors rather than bacterial viability, thereby reducing selective pressure for resistance and enhancing the efficacy of combination treatments. Quorum sensing (QS), the cell-to-cell communication system governing biofilm formation, virulence factor production, and antimicrobial resistance, represents an attractive target in this context, as its interference can reduce bacterial pathogenicity and restore antibiotic susceptibility.[1][2]

Following a rational drug design strategy, three complementary medicinal chemistry campaigns were pursued. A first series of candidates was identified through structure-based virtual screening. A second series originated from structure-based optimization of an in-house, previously identified QS inhibitor hit,[3] in which systematic modifications defined the SAR around the parent scaffold. A third series was generated via field-based scaffold-hopping to expand chemical diversity.

All compounds were initially evaluated for their ability to inhibit biofilm formation in *S. aureus* and *P. aeruginosa*, representative Gram-positive and Gram-negative ESKAPE pathogens, and for their capacity to quench QS signaling in *Vibrio harveyi* reporter strains without affecting bacterial viability.

This screening campaign led to the selection of compounds, across different chemotypes, displaying antibiofilm activity against both strains with MBIC₅₀ in the low micromolar range; these compounds underwent in-depth microbiological profiling of their antivirulence potential.[4] In *S. aureus*, the selected compounds reduced the production of α -hemolysin and protein A, and impaired bacterial adhesion to human epithelial cells through decreased expression of MSCRAMM adhesins. In co-culture with *S. aureus*, the same compounds reduced *P. aeruginosa* pyocyanin and elastase production in a dose-dependent manner. No cytotoxicity was observed either in vitro (A549 cells) or in vivo (*Galleria mellonella* model).[5] For the most promising compound emerging from the scaffold-hopping series and active against *S. aureus*, additional studies addressed its efficacy in inhibiting biofilm formation in clinical isolates and its ability to potentiate antibiotic activity in combination treatments.[6]

Overall, this work delivers a diversified portfolio of QS inhibitors with validated antibiofilm and antivirulence profiles, supporting their further development as adjuvant anti-infective agents against multidrug-resistant pathogens.

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OC03

IMAGING AND TARGETING LOW OXYGEN LEVELS IN TUMOURS

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In both solid and hematological malignancies, conditions of lower-than-normal oxygen content, defined as hypoxia, dictate the fate of patients. In solid tumours, hypoxia can span from 4 to 0.1% O₂ and promotes resistance to conventional chemotherapeutic agents and radiotherapy, aggressiveness, progression, recurrency and metastatization.¹ For these reasons, hypoxia-activated prodrugs (HAPs) have been proposed to selectively eradicate the hypoxic cells and increase the therapeutic window of chemotherapy,² targeted therapy,³ and PROTACs.⁴ Yet, despite HAPs progressed to the clinical phases, none has been approved. Among the reasons underlying their failure, there is a paucity of tools to detect and study hypoxia at the preclinical levels and in humans. For instance, current probes only visualize O₂ levels below 1% (e.g. 18-FMISO), rely on indirect antibody-based methods (e.g. pimonidazole) or are visualized by fluorescence that do not allow *in vivo* detection.

By taking advantage of the versatility of the tetrazine-dienophile reaction, we have developed probes that mitigate most of the limitations of current tools. In detail, we developed 2-nitroimidazole baits for the pre-targeting of hypoxia that can be clicked with fluorescent tetrazines (Figure 1).⁵ By merging a ligation and a click-to-release approach, we were able to discriminate the hypoxic core of 3D models and the areas in which the released probe had diffused, quantifying the by-stander effect. In our quest, we identified both 2-nitroimidazole baits to visualize moderate (<4% O₂) or severe hypoxia (<2% O₂). Moreover, our probes detect hypoxia in multiple preclinical models, from monolayer cells to 3D spheroids and patient-derived organoids. We demonstrated that this latter model, widely used to study interpatient variability, naturally develops hypoxic regions. Given the compatibility of the tetrazine-dienophile reaction with living organisms, our baits can be also used to visualize hypoxia *in vivo*, by clicking them with appropriately functionalized tetrazines (e.g. detectable by NIR or MRI). Last, applications of the 2-nitroimidazole baits to release chemotherapeutic drugs selectively in the tumour from tetrazine-caged prodrugs are currently being developed.

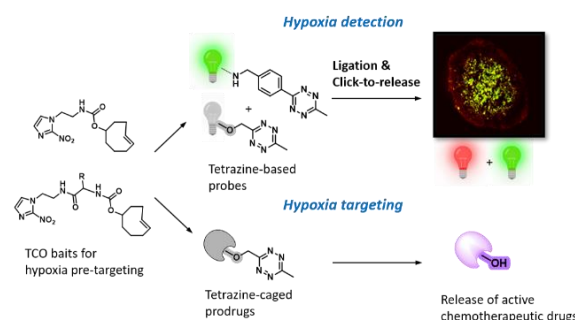


Figure 1. Approaches to visualize and target hypoxia in tumours.

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OC04

Cu(I)-BASED ANTIBODY-DRUG CONJUGATES: A NOVEL PLATFORM FOR CANCER THERANOSTICS

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Antibody-drug conjugates (ADCs) are a rapidly growing class of targeted pharmaceuticals that enable selective delivery of highly potent cytotoxic agents to tumor cells while limiting systemic toxicity. However, their broader clinical potential is still constrained by the limited diversity of available payloads and the emergence of resistance mechanisms, highlighting the need for novel cytotoxic scaffolds with alternative mechanisms of action.¹ In this context, metal-based compounds offer unique opportunities to enrich the payload toolbox beyond conventional organic drugs, thanks to the versatility of their coordination chemistry. Among them, copper complexes are particularly attractive due to dysregulated copper homeostasis in tumor cells, which promotes their intracellular accumulation. This feature can be exploited to achieve selective cytotoxicity in cancer cells while maintaining a favourable toxicity profile.^{2,3} In addition, copper-based systems are attracting growing interest in nuclear medicine due to the unique properties of the Cu-64/67 radionuclide pair, which represents an ideal match for theranostic applications, enabling the combination of positron emission tomography (PET) imaging and β^- -based radiotherapy.⁴

We previously developed a novel class of Cu(I) phosphino complexes with potent anticancer activity across 2D/3D tumor models, including resistant variants. SARs identified key ligand-dependent features, while PDI emerged as a potential target linked to a non-classical cell death pathway. Lead compounds also showed significant in vivo efficacy in murine solid tumor models. Based on these findings, a bis(3,5-dimethylpyrazol-1-yl)acetic acid (L1) scaffold was selected as a versatile co-chelating platform for antibody lysine conjugation. Trastuzumab was used as targeting vector due to its high affinity for HER2-overexpressing tumors. The corresponding L1-based derivative was successfully conjugated to the antibody, affording stable bioconjugates that retained high binding affinity toward their antigen. As a preliminary evaluation of their theranostic potential, the trastuzumab-based ADCs were radiolabeled with Cu-64. PET/CT imaging in HER2-positive tumor xenografts demonstrated tumor accumulation over time, supporting the potential of Cu-based ADCs for targeted cancer applications.

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OC05

UNTARGETED DIVERSITY-ORIENTED SYNTHESIS (UnDOS) FOR THE IDENTIFICATION OF NOVEL ANTITUMOR AGENTS: AN INTEGRATED APPROACH OF IVS, BIOINFORMATICS AND OMICS FOR TARGETS DECONVOLUTION

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Despite significant advances in cancer therapy, the identification of new pharmacological strategies remains a major challenge [1]. Diversity-Oriented Synthesis (DOS) has emerged as a valuable strategy for the discovery of novel anticancer agents, enabling the generation of structurally diverse compounds that serve both as chemical probes and as promising candidates for cancer therapy [2, 3]. In this work, we describe the application of an Untargeted DOS (UnDOS) substrate-based approach, aiming to identify novel antitumor compounds and elucidate their associated biological targets [4]. Selecting an *L*-amino acid as common reagent, we designed and synthesized a set of twenty small molecules - containing ten different privileged molecular scaffolds - which were phenotypically screened against a broad panel of tumor cell lines.

Among the synthesized derivatives, compounds **31** and **63** were selected for further investigation based on their micromolar antiproliferative activity and selectivity against the A-375 melanoma cell line. To identify the binding partners and clarify the mechanism underlying the observed effects, an integrated workflow combining inverse virtual screening (IVS), bioinformatics, and multi-omics analyses was employed. Predicted targets were prioritized according to their expression levels in A-375 cells relative to healthy HaCaT keratinocytes. The most relevant candidates emerging from the integrated analyses were subsequently validated through binding, functional, and cellular assays, which confirmed measurable interactions with several targets and highlighted Transient Receptor Potential (TRP) channels and Bromodomain-containing Protein 4 (BRD4) as key mediators of the observed biological effects. In-cell studies further demonstrated that both compounds exert pro-apoptotic activity and promote protein misfolding and oxidative stress, providing additional support for their antitumor mechanism of action. Besides the identification of novel and promising antitumor agents, one of the most relevant impacts of this work is to provide a generic and versatile workflow for the target deconvolution process that can be appropriately modulated depending on the biological activity being studied.

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7 N 15 P 6 C 9 F 17

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OC06

5-(3',4'-DIHYDROXYPHENYL)- γ -VALEROLACTONE-SULFATE AS AN INFLAMMATION-TRIGGERED PRODRUG FOR TARGETED NRF2 ACTIVATIONDella Vedova L.¹, Gado F.¹, Ferrisi R.¹, Mauri A.¹, Taheribaviliolyaei R.¹, Messinese S.¹, Bassi A.¹, Manzi S.¹, Altomare A.¹, Dallanocce C.¹, Aldini G.¹, Baron G.¹¹Department of Pharmaceutical Sciences, University of Milan, Via Mangiagalli 25, 20133 Milan, Italy
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Nuclear factor erythroid 2–related factor 2 (Nrf2) plays a central role in cellular defense against oxidative stress and inflammation, making it an attractive therapeutic target in chronic inflammatory disorders [1]. Nevertheless, the majority of currently available Nrf2 activators act through nonspecific electrophilic interactions that may result in poor selectivity and undesirable off-target effects [2]. The microbial-derived flavan-3-ol metabolite 5-(3',4'-dihydroxyphenyl)- γ -valerolactone (VL) is capable of activating Nrf2 through oxidation of its catechol moiety and subsequent modification of Keap1. In vivo, however, VL is rapidly converted into its sulfate conjugate, 5-(3',4'-dihydroxyphenyl)- γ -valerolactone sulfate (VLS), a metabolite expected to display reduced reactivity due to masking of the catechol group [3]. In this study, we explored the hypothesis that VLS may act as an inflammation-sensitive precursor capable of regenerating the active metabolite under inflammatory conditions. Chemically synthesized VLS was tested in a TNF α -induced HEK293T Nrf2 reporter system. Whereas no significant activity was observed under basal conditions, inflammatory stimulation markedly enhanced Nrf2 activation by VLS. To further investigate this response, intracellular VLS concentrations were quantified by LC–MS/MS. TNF α exposure resulted in a significant decrease in intracellular VLS levels, suggesting inflammation-dependent metabolic processing of the conjugate. Consistently, ELISA analysis demonstrated a transient increase in Arylsulfatase A (ARSA) following TNF α treatment, supporting the possible involvement of sulfatase-mediated desulfation in the activation process. Collectively, these results indicate that sulfation may function as a reversible masking strategy that limits catechol reactivity during circulation while allowing selective release of the active species in inflamed tissues. This work highlights enzyme-triggered activation of redox-active metabolites as a potential strategy to achieve localized and context-dependent Nrf2 modulation.

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OC07

DEVELOPMENT OF A GUT-RESTRICTED NLRP3 INHIBITOR FOR IBD: FROM DESIGN TO IN VIVO EFFICACY

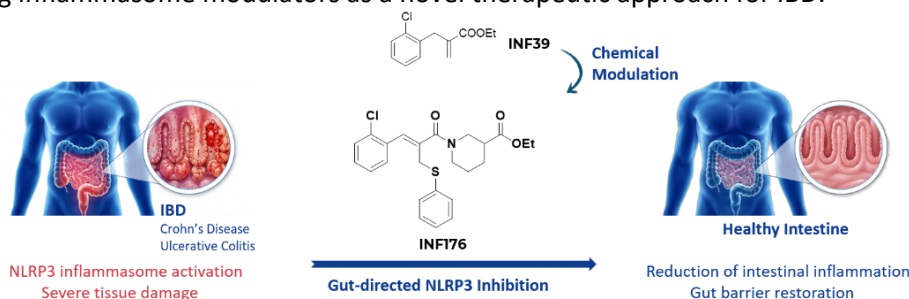
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Inflammatory Bowel Disease (IBD), including Crohn's Disease (CD) and ulcerative colitis (UC), are chronic and relapsing inflammatory disorders of the gastrointestinal tract. Although the pathophysiology of IBD is complex and not yet fully elucidated, increasing evidence supports a key role of the innate immune response in disease onset and progression [1,2]. In this context, the NLRP3 inflammasome has emerged as a pivotal driver of intestinal inflammation through the activation of caspase-1 and the subsequent release of pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-18. Targeting NLRP3 represents a promising therapeutic strategy [3,4]; however, most reported inhibitors act systemically and may be associated with undesired immunosuppressive effects. Here, we describe the design and development of a novel gut-restricted NLRP3 inhibitor, INF176, obtained through structural optimization of INF39, a previously developed acrylate scaffold [5]. INF176 inhibited IL-1 β release in both human and murine macrophages in a dose-dependent manner, with IC₅₀ values of 5.90 $\pm$ 0.70 μ M and 6.53 $\pm$ 1.18 μ M, respectively, and reduced ASC speck formation by 37% in THP-1 cells, confirming effective modulation of NLRP3 activation. *Ex vivo* permeability studies demonstrated a gut-restricted profile, with significant accumulation in intestinal tissues (82-96 μ g/g tissue) and colon (48 $\pm$ 4 μ g/g tissue). Consistently, pharmacokinetic analysis revealed very low oral bioavailability (F < 3%), comparable to that of sulfasalazine, a reference non-systemic drug for IBD. Importantly, INF176 significantly ameliorated disease severity in a DSS-induced mouse model of colitis, by (i) reducing NLRP3-mediated signaling and resulting intestinal inflammation, (ii) improving systemic and tissue parameters, (iii) decreasing histological damage, and (iv) restoring epithelial barrier integrity. Overall, these findings identify INF176 as a promising gut-restricted NLRP3 inhibitor and support the development of locally acting inflammasome modulators as a novel therapeutic approach for IBD.



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OC08

A TUNABLE CARNOSINE–HNE MICHAEL ADDUCT RESTORES REDOX–INFLAMMATORY BALANCE BY MODULATING THE Nrf2–NF-κB AXIS

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Nuclear factor erythroid 2–related factor 2 (Nrf2) is a master regulator of antioxidant and cytoprotective responses and represents an attractive therapeutic target. Most Nrf2 activators under clinical investigation are electrophilic molecules that covalently modify Keap1 cysteine residues. However, their nonspecific reactivity may cause off-target toxicity and idiosyncratic adverse reactions linked to irreversible protein adduction. In contrast, endogenous electrophilic mediators generated during oxidative stress, such as the lipid peroxidation product 4-hydroxynonenal (HNE), act as physiological Nrf2 activators and provide a validated model of redox signaling. As endogenous ("self") metabolites, they are integrated into physiological adaptive responses and may exhibit a lower propensity to trigger immune-mediated idiosyncratic reactions than xenobiotic electrophiles. Nevertheless, their high reactivity, cytotoxicity, and poor drug-like properties preclude therapeutic use. To bridge this gap, we designed a strategy aimed at preserving endogenous electrophile signaling while overcoming its intrinsic liabilities. Specifically, we investigated the carnosine–HNE Michael adduct (CAR–HNE) as a metabolically stable, redox-active reservoir of electrophilic equivalents. After synthesis and full characterization, CAR–HNE was evaluated for physicochemical stability, metabolic fate, thiol reactivity, and biological activity. The adduct showed high stability in biological matrices while retaining tunable thiol reactivity, consistent with Keap1 modification and downstream Nrf2 activation. In cell-based assays, CAR–HNE dose-dependently activated Nrf2 signaling and inhibited NF-κB activity, without the cytotoxicity observed for equimolar free HNE. This electrophile-transfer strategy was then evaluated in a murine model of DSS-induced colitis, characterized by dysregulated redox homeostasis and chronic inflammation. CAR–HNE significantly reduced inflammation and outperformed equimolar carnosine and HNE supporting the adduct itself as the bioactive species. To gain mechanistic insight, colon tissues were analyzed by label-free quantitative proteomics using nanoLC–HRMS/MS on an Orbitrap Fusion Tribrid platform. Proteomic and pathway analyses revealed activation of Nrf2-regulated antioxidant and detoxification programs, including glutathione-related pathways, with attenuation of inflammation-associated signaling networks. Targeted quantitative proteomics using the ProteomeEdge DiscoveryEdge175 kit on an ExionLC–ZENO-TOF platform further supported inflammatory and redox-related readouts. Collectively, these results identify CAR–HNE as a metabolically stable HNE-derived electrophile reservoir capable of controlled Nrf2 activation. This work establishes a medicinal chemistry paradigm in which endogenous reactive carbonyl species are transformed into tunable redox-active entities with improved pharmacological properties and reduced toxicological liabilities, providing a platform for redox-modulating therapeutics [1].

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OC09

**LC-MS PROFILING OF HISTONE PTMS IN ALZHEIMER'S DISEASE MOUSE MODEL ASTROCYTES:
TOWARD EARLY DIAGNOSIS AND TARGETED NEUROPROTECTION**De Simone A.^a, Esposito E.^b, Grolla A.^c, Cavallo M.^d, Casali C.^d, Lim D.^c, Tapella L.^c, Naldi M.^e, Fiori J.^{b,f}^a University of Turin, Department of Drug Science and Technology, via P.Giuria 9, 10125 – Turin^b IRCCS Istituto delle Scienze Neurologiche, Bellaria Hospital, via Altura 3, 40139 – Bologna^c Università degli Studi del Piemonte Orientale, Department of Pharmaceutical Sciences, via Bovio 6, 28100 – Novara^d University of Pavia, Department of Biology and Biotechnology "Lazzaro Spallanzani", via Ferrata 9, 27100 – Pavia^e University of Bologna, Department of Pharmacy and Biotechnology, via Belmeloro 6, 40126 – Bologna^f University of Bologna, Department of Chemistry "G. Ciamician", via Selmi 2, 40126 – Bologna
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Epigenetic mechanisms, including histone post-translational modifications (PTMs), play a central role in regulating gene expression and chromatin organization in the central nervous system. Increasing evidence indicates that dysregulation of histone modifications contributes to the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), by altering transcriptional programs and cellular responses to stress. [1-3] In parallel, astrocytes have emerged as key regulators of brain function and disease, with their activity and reactivity tightly controlled by dynamic epigenetic programs. [4] However, the molecular characterization of histone PTMs in astrocytes remains limited, particularly at the proteoform level. In this study, we developed and applied integrated top-down and bottom-up LC-MS workflows to profile histone PTMs in immortalized astrocytes derived from a 3xTg-AD mouse model (3xTg-iAstro) [5] and wild-type control (WT-iAstro). Histones were isolated from nuclear fractions and analysed by high-resolution mass spectrometry (HRMS) enabling the assessment of intact histone proteoforms together with site-specific PTMs localization. Comparative analysis revealed a distinct phosphorylation profile in AD mouse model astrocytes, characterized by increased phosphorylation of linker histone H1 variants (H1.1 and H1.2) and reduced phosphorylation of H2A.X, a key component of the DNA damage response. [6] These alterations are consistent with a shift toward chromatin compaction and altered chromatin responsiveness, as established by microscopy investigation. Overall, this study highlights the power of integrated MS-based approaches for the comprehensive characterization of histone PTMs, provides new insights into astrocyte epigenetic dysregulation in AD, and supports the identification of disease-associated PTMs patterns as potential epigenetic biomarkers for early diagnosis and targeted intervention.

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OC10

TUNING MULTITARGET DRUG DESIGN BASED ON CARBONIC ANHYDRASE MODULATION FOR THE TREATMENT OF MULTIFACTORIAL PATHOLOGIES

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Combination therapies have long been clinically established as effective treatments for multifactorial diseases because of the concurrent engagement of multiple biological targets [1]. In recent years, medicinal chemistry has increasingly focused on multi-target directed ligands (MTDLs) as single-molecule alternatives with the potential to combine efficacy with improved pharmacokinetic properties, reduced drug–drug interactions, and enhanced synergistic effects [1-3]. Over recent years, we have applied structure-based drug design strategies to develop MTDLs tuned around carbonic anhydrase (CA) modulation toward a broad range of pathological conditions [4-11]. Promising candidates showed dual or multitarget activity in multiple disease settings, including *in vivo* models of glaucoma, inflammation, memory disorders, cancer, infections, and neurodegeneration, consistently outperforming the corresponding single-target agents and their combinations. Overall, carbonic anhydrase modulators have emerged as adaptable building blocks for multitarget drug design in multifactorial pathologies, supporting the development of integrated therapeutic strategies for complex diseases.

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OC11

ULTRAFAST GRAPH RECOGNITION (UGR): A GRAPH-BASED MOLECULAR SIMILARITY METHOD FOR LIGAND-BASED VIRTUAL SCREENING

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The continuous growth of drug-like chemical libraries is renewing interest in fast virtual screening approaches for early hit identification. Ligand-based similarity methods play a key role in this context, as they enable the rapid prioritization of compounds based on known active ligands while remaining largely independent of target structural information. Among these approaches, Ultrafast Shape Recognition (USR) introduced an efficient, alignment-free strategy for 3D molecular shape comparison, achieving good performance in virtual screening [1]. However, USR still relies on 3D conformer generation, which represents a major bottleneck in terms of computational cost and can negatively affect performance when the selected conformation does not reflect the bioactive geometry. Moreover, results depend on the accurate coverage of the conformational space of each ligand, which can be challenging for more complex molecular structures.

To overcome these limitations, we developed Ultrafast Graph Recognition (UGR), a new ligand-based molecular similarity method that replaces geometric distances with topological distances derived from molecular graph representations. UGR follows the same conceptual framework and statistical formulation originally introduced for USR, but operates entirely in graph space, eliminating the need for conformer generation while retaining ultrafast descriptor calculation and comparison.

Similarly to USR-derived methods such as USRCAT and ElectroShape, UGR can incorporate pharmacophoric and electrostatic information [2,3]. In addition, UGR supports an extended set of pharmacophoric features and allows the use of different partial charge models, increasing its flexibility for diverse screening scenarios.

UGR performance was assessed through a retrospective virtual screening benchmark on 100 targets from the Directory of Useful Decoys, Enhanced (DUD-E) dataset and compared to USR, USRCAT, and ElectroShape [4]. When pharmacophoric features were included, UGR showed consistently improved enrichment, achieving overall average enrichment factors (EF) of 22.27 at the 0.25% level, compared to 8.84, 15.64, and 14.48 for USR, USRCAT, and ElectroShape, respectively. UGR also yielded higher per-target EF_{0.25%} values for most targets. Furthermore, the Python implementation of UGR achieved screening rates of 100–200 compounds per second, substantially faster than RDKit-based USR and USRCAT workflows (20–30 compounds per second).

Overall, UGR removes the dependence on 3D conformer generation while improving enrichment performance and maintaining speed and scaffold-hopping capability, providing an efficient alternative for ligand-based virtual screening and hit/derivative identification.

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OC12

MOLECULAR DYNAMICS STUDY OF ATG13 UBIQUITYLATION IN ULK1 STRUCTURAL DYNAMICS AND ASSEMBLY OF AUTOPHAGY INITIATION COMPLEX

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Ubiquitylation is a key post-translational modification regulating protein stability and function across multiple cellular pathways. The E3 ubiquitin ligase Praja2, activated downstream of the GPCR–cAMP signaling cascade, has been implicated in the modulation of autophagy through interactions with components of the ULK1 complex. Autophagy is a conserved homeostatic process responsible for the degradation of damaged or superfluous cellular components. Its initiation is controlled by the ULK1 complex, composed of ULK1, ATG13, ATG101, and FIP200, which integrates upstream signaling cues into autophagosome formation. [1,2]

Recent evidence indicates that Praja2 mediates non-proteolytic ubiquitylation of ATG13 at lysine 504, suggesting a regulatory role for this modification in autophagy activation (Figure 1).

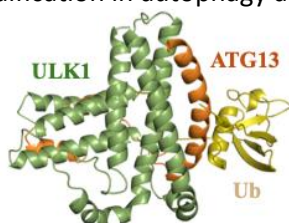


Figure 1. Cartoon representation of ULK1 (green) in complex with ATG13 (orange) and ubiquitin (yellow).

Here, we employed microsecond-scale molecular dynamics (MD) simulations to investigate the structural and dynamical effects of ATG13 ubiquitylation on ULK1 and on the assembly of the autophagy initiation complex. Comparative analyses of ULK1 alone, the ULK1/ATG13 complex, and the ubiquitylated ATG13 system, and the corresponding ULK1/ATG13/FIP200 complexes revealed that ubiquitylation at K504 induces significant conformational rearrangement within the ULK1 C-terminal domain. Moreover, simulations of FIP200-containing complexes showed that ATG13 ubiquitylation reshapes ULK1 collective motions and redirects allosteric communication pathways, generating conformational states compatible with productive higher-order complex assembly. Overall, our findings support a model in which Praja2-driven ubiquitylation of ATG13 acts as an allosteric molecular switch that regulates ULK1 conformational dynamics and promotes assembly-competent states of the autophagy initiation complex. Importantly, these computational observations are supported by complementary experimental validation, providing convergent evidence for a functional role of ATG13 ubiquitylation in regulating ULK1 complex assembly and autophagy initiation.

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OC13

HARNESSING MULTI-TARGET DRUG DISCOVERY FOR CIRCADIAN CLOCK DYSFUNCTION IN ALZHEIMER'S DISEASE

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Circadian clock dysfunction is increasingly recognized as a key contributor to Alzheimer's disease (AD) [1], making circadian modulation an attractive therapeutic strategy. In this context, polypharmacology enables the simultaneous targeting of interconnected circadian and disease-associated pathways through a single molecular entity [2].

We employed an iterative, structure-guided medicinal chemistry approach to develop multi-target-directed ligands (MTDLs) targeting two central regulatory kinases, glycogen synthase kinase-3 β (GSK3 β) and casein kinase 1 δ (CK1 δ), which play pivotal roles in both circadian regulation and neurodegenerative processes. Initial ligand-based and docking studies identified the maleimide scaffold as a promising starting point for dual CK1 δ /GSK3 β inhibition (Figure 1). This was followed

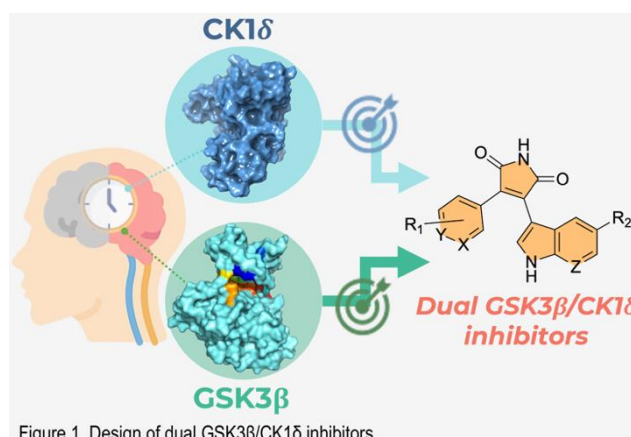


Figure 1. Design of dual GSK3 β /CK1 δ inhibitors.

by the development of an efficient and versatile synthetic methodology enabling rapid access to maleimide-based analogues and systematic structure-activity relationship (SAR) exploration. Two successive subsets of MTDLs were developed and optimized to improve physicochemical properties and dual GSK3 β /CK1 δ inhibitory activity. This iterative optimization led to two brain-penetrant compounds with favorable aqueous solubility and microsomal stability. One compound exhibited a well-balanced dual profile (IC_{50} GSK3 β = 1.95 μ M; IC_{50} CK1 δ = 1.98 μ M), whereas a second analogue showed enhanced GSK3 β potency while retaining CK1 δ activity (IC_{50} GSK3 β = 0.20 μ M; IC_{50} CK1 δ = 1.08 μ M). Both candidates progressed through in vitro cytotoxicity assays and cellular models assessing circadian and neurodegeneration-related modulation, while kinase selectivity profiling and *Drosophila melanogaster* toxicity studies are ongoing. Collectively, these compounds represent the first circadian-directed MTDLs capable of simultaneously modulating the GSK3 β /CK1 δ signaling axis, providing an innovative polypharmacological strategy aimed at counteracting circadian clock dysfunctions in AD.

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OC14

SMALL MOLECULES TARGETING THE HUR-RNA COMPLEXES: AN INNOVATIVE STRATEGY TO DISCOVER ANTICANCER AGENTS

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The Human antigen R (HuR) protein is an RNA-binding protein involved in multiple hallmarks of tumorigenesis (i.e. cell proliferation, angiogenesis, immune response and metastasis). Therefore, interfering with the formation of HuR-RNA complexes has emerged as an innovative and promising strategy for cancer treatment. Our research group has identified a series of small molecules able to bind HuR and potentially interfering with the stabilization of oncogenic mRNAs [1]. In the present work, we expanded our benzyl-resorcinol arylamide (BRAC) HuR-binding chemotype by incorporating heteroaromatic fragments previously identified through protein-templated dynamic combinatorial chemistry (pt-DCC) [2]. A focused library of new derivatives was designed (Figure 1) and synthesized with an eye to green chemistry, and subsequently evaluated for antiproliferative activity across eight cancer cell lines, including breast, lung and gliomas. Four compounds showed broader and enhanced antitumor activity, with IC₅₀ values as low as 24 μM. STD-NMR interaction and competition assays confirmed specific HuR interaction, with compound BRAC-9 retaining binding under PNA competition. Docking studies showed that all compounds maintained a conserved interaction pattern with key residues of the binding pocket, while MM-GBSA calculations and MD simulations suggested that the complexes with HuR are stable and energetically favorable, providing a rationalization of the experimental results and valuable insights for future development of a new generation of analogues with improved potency and drug-likeness.

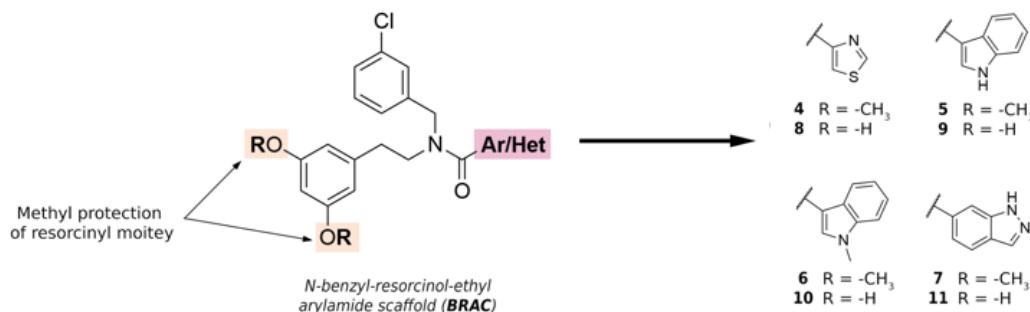


Figure 1. Chemical structures of the new derivatives of the BRAC scaffold.

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Nuove Prospettive in Chimica Farmaceutica

OC15

UNLOCKING NEUROPROTECTION: RATIONAL DESIGN AND SYNTHESIS OF $\sigma 1R$ AGONISTS FOR HUNTINGTON'S DISEASE TREATMENT

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a mutation in the HTT gene, leading to the progressive degeneration and death of neurons in specific brain regions. No effective therapies are currently available to halt or prevent the onset of this devastating disease. However, in recent years a growing number of studies has highlighted the potential role of the sigma-1 receptor ($\sigma 1R$) in modulating various neurodegenerative processes, including those associated with HD¹. The $\sigma 1R$ is a small and poorly understood membrane receptor expressed in the central nervous system. Substantial evidence has shown that agonists have neuroprotective activity in neurodegenerative diseases. Nevertheless, the structural basis for agonism or antagonism on $\sigma 1R$ is largely unknown. In general, the overall conformation of the receptor bound to the agonist crystallizes similarly to that bound to the antagonist, except for a shift of about 1.8Å in the $\alpha 4$ helix². Probably, this shift is responsible for the tendency of agonists to decrease the oligomeric state of the protein and can be used as a discriminator for classification into agonist. Through molecular dynamics simulations, we identified the key receptor-ligand interactions stabilizing the inactive multimeric state of $\sigma 1R$. Based on these computational insights, we designed and synthesized a library of novel small molecules. The project originated from a known drug possessing high affinity for $\sigma 1R$ but lacking the desired functional agonistic profile³. The design strategy purposely avoided specific structural features of the parent drug, introducing instead geometrical modifications aimed at sterically disrupting the multimerization interface to trigger receptor activation. Specifically, these modifications were designed to sterically clash with the $\alpha 4$ helix and destabilize the GXXXG motif, forcing receptor monomerization⁴. Concurrently, the newly synthesized compounds were evaluated through a comprehensive pharmacological pipeline. Following *in vitro* binding affinity assays for $\sigma 1R$ and *in cellulo* functional characterization, the neuroprotective effects of our lead were investigated *in vivo* in a 3-nitropropionic acid (3-NP) mouse model of HD. In this 4-day acute study, histological analysis of striatal cryosections demonstrated that the lead compound (0.5-1.5 mg/kg) demonstrated profound, dose-dependent, strictly $\sigma 1R$ -mediated neuroprotection (reducing striatal lesions 57%, Caspase-1 64%) and anti-inflammatory action (suppressing NF- κ B/NLRP-3 by 52-68%, and IL-1/IL-6/TNF α by 54-90%). Crucially, the co-administration of a known $\sigma 1R$ antagonist almost entirely reversed these neuroprotective effects, unambiguously confirming that the *in vivo* efficacy of the lead is strictly $\sigma 1R$ -mediated. Comparison across the experimental groups confirmed that while the acid-only group exhibited extensive striatal lesions, treatment with the lead compound effectively preserved neuronal integrity, with no inherent toxicity observed in the lead-only control group. The data coming from all these studies will be shown and discussed.

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OC16

FROM PHENOTYPIC SCREENING TO TARGET NETWORKS: A POLYPHARMACOLOGY-ORIENTED APPROACH FOR RETT SYNDROME THERAPEUTICSTongiori E.^a, Berutto V.^a, Ciraci V.^a, Prado Romero D.L.^b, Gualandi N.^c, Roggero O.M.^d, Carosati E.^b^a Department of Life Sciences, University of Trieste, Via Weiss 2, 34127, Trieste, Italy^b Department of Chemical and Pharmaceutical Sciences, University of Trieste, Via L-Giorgieri 1, 34127, Trieste, Italy^c Department of Medicine, University of Udine, via Colugna, 50, 33100, Udine, Italy^d Department of Medical Biotechnology and Translational Medicine, University of Milan, Segrate, 20054, Milan, Italy

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Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily caused by loss-of-function mutations in the X-linked MECP2 gene, leading to progressive neuronal atrophy and dysfunction of neuronal networks. Although several compounds have shown beneficial effects in phenotypic assays, their molecular mechanisms of action remain largely unexplored, limiting the development of rational therapeutic strategies.

To investigate the pharmacological pathways underlying neuronal rescue, an established in vitro model of primary hippocampal neurons derived from RTT mice was employed in a phenotypic screening involving approximately 640 FDA-approved drugs. Fourteen compounds were identified as active hits based on their ability to rescue neuronal atrophy and were subsequently characterized using five complementary morphological descriptors, including total dendritic length, polarization index, Sholl crossings, distal dendrites, and maximal dendritic length. Five compounds emerged as the most effective, restoring multiple morphological parameters to levels comparable to those achieved by the internal positive control mirtazapine.

To elucidate their potential mechanisms of action, a large-scale structure-based target deconvolution strategy was implemented using BioGPS, a computational platform capable of screening the human pocketome, comprising more than 25,000 ligand-bound binding pockets derived from over 210,000 experimentally determined human protein structures available in the Protein Data Bank. Unlike conventional target-fishing approaches focused on single compounds, this study required a multi-compound/multi-target analysis. To address this challenge, a novel double-normalization procedure was developed, generating ZZscores that quantify ligand-pocket complementarity while accounting for both compound-specific and pocket-specific score distributions.

The analysis revealed that the most active compounds displayed significantly broader and partially overlapping target profiles compared with inactive controls, supporting a polypharmacological mode of action. Moreover, similarities between phenotypic rescue patterns and predicted target profiles enabled the identification of shared proteins and signaling pathways potentially involved in neuronal recovery. These findings suggest that effective RTT treatments may require simultaneous modulation of multiple biological targets rather than highly selective therapeutic approaches.

We present the in vitro-in silico framework, that integrates phenotypic screening, structure-based target prediction, and network-level analysis, and the results to confirm the hypothesized target(s).

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OC17

FROM FUNGAL METABOLITES TO MULTI-TARGET LIGANDS: A NATURE-INSPIRED AND GREEN SEMI-SYNTHETIC STRATEGY FOR ALZHEIMER'S DISEASE DRUG DISCOVERY

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The funded NInFA (Nature-Inspired structures: Fungal metabolites for a sustainable semi-synthetic approach to the discovery of new multi-target anti-Alzheimer's drugs) project [1] addressed the urgent need for innovative therapeutic strategies against Alzheimer's disease (AD). The acronym, derived from the Greek "νύμφη" (minor deities of nature), reflects the central role of nature as both inspiration for drug design and a source of bioactive compounds [2]. Building on previous studies conducted by the participating research groups [3,4], and supported by international collaborations (University of Lisbon and University of Vienna), the project delivered a series of new chemical entities with multi-target activity (multi-target-directed ligands, MTDLs) acting on key pathological pathways involved in AD. Molecular design combined fungal secondary metabolites (ochratoxin α , OT α , and ochratoxin β , OT β) with synthetic moieties inspired by approved anti-AD drugs (rivastigmine and donepezil), through linking and fusing strategies guided by in silico approaches. These hybrid compounds were successfully synthesized, structurally characterized, and biologically evaluated across both established (ChEs) and emerging targets (GSK-3 β , FAAH), as well as for their antioxidant activity and metal-chelating properties. The preparation of MTDLs was further optimized under green chemistry conditions (including deep eutectic solvents (DESs), alcoholic media, and solvent-free systems), both for the extraction of natural metabolites and for synthesis, thereby enhancing the sustainability of the process. Selected compounds exhibited promising biological profiles, supported by preliminary pharmacokinetic characterization, identifying valuable hit candidates for further development. Representative chemical structures of the most relevant compounds are shown in Figure 1.



Figure 1. Chemical structures of donepezil–OT α /OT β (left) and rivastigmine–OT α /OT β (right) hybrid compounds.
X= H, Cl

References:

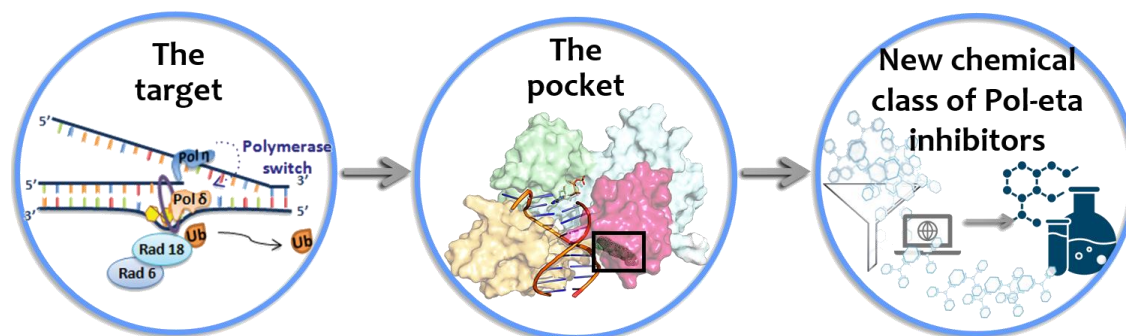
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OC18

DISCOVERY AND DEVELOPMENT OF NOVEL POLYMERASE η INHIBITORS TO OVERCOME CANCER DRUG RESISTANCE

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Polymerase η (Pol- η) is a specialized polymerase involved in translesion DNA synthesis, enabling replication across damaged DNA. While essential in normal cells, Pol- η promotes mutagenesis and supports replication under cancer-related and chemotherapy-induced stress (e.g., cisplatin, gemcitabine), contributing to drug resistance in aggressive tumors such as melanoma, head and neck, and ovarian cancers. Targeting Pol- η with small molecules represents a promising strategy to overcome resistance.^{1,2} Despite its relevance, Pol- η remains largely unexplored as therapeutic target. Here, we report the identification of a first class of 35 natural-like inhibitors of Pol- η . The resulting structure-activity relationship elucidates the key structural features that enhance the potency and the drug-like profile of our new derivatives. Indeed, ARN24964 emerged as a valuable compound, exhibiting an IC_{50} value of 14.7 μ M against Pol- η and significant synergistic effect in combination with cisplatin in Pol- η -proficient cancer cell lines (A375, A549, OVCAR3). Although ARN24964 showed good solubility and high plasma and Phase I microsomal stability, it is limited by poor Phase II microsomal stability.³ Building on these results, we are developing a new class of non-natural inhibitors of ARN24964 with improved drug-like properties using a structure-based drug design approach (Figure 1). These results highlight Pol- η inhibition as a viable strategy to overcome drug resistance in relapse-prone cancers.



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OC19

DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF DIHYDROTRIAZINE-BASED ANTIFOLATES AGAINST *TRYPANOSOMA BRUCEI*

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Neglected tropical diseases (NTDs), including human African trypanosomiasis (HAT), still represent a major global health burden, with limited therapeutic options characterized by toxicity, poor compliance, and emerging resistance [1]. Targeting folate metabolism through the inhibition of *Trypanosoma brucei* dihydrofolate reductase (*Tb*DHFR) and pteridine reductase 1 (*Tb*PTR1) is a validated strategy to overcome metabolic bypass mechanisms and improve antiparasitic efficacy [2]. Pursuing our efforts in the search of novel anti-*T. brucei* agents targeting folate metabolism [3,4], we developed a novel series of substituted dihydrotriazines bearing PABA-mimetic moieties and diversified aromatic side chains, aiming at dual *Tb*DHFR/*Tb*PTR1 inhibition. Enzymatic evaluation has showed that the compounds can inhibit *Tb*DHFR in the low micromolar range ($K_i = 0.54\text{--}16.4\text{ }\mu\text{M}$), while displaying lower affinity toward *Tb*PTR1 ($K_i = 5.35\text{--}218\text{ }\mu\text{M}$). The observed activity against *h*DHFR ($K_i = 0.35\text{--}3.27\text{ }\mu\text{M}$) highlights the need for optimization in terms of potency and selectivity. Despite exhibiting modest antiparasitic activity in cell-based assays at 100 μM , a subset of compounds showed an interesting behaviour in combination tests with the antifolate drug methotrexate (MTX), significantly enhancing its trypanocidal effect on *T. brucei* up to 10-fold. Docking studies and molecular dynamic simulations of the novel compounds in complex with *Tb*DHFR, *Tb*PTR1, and *h*DHFR suggested that the dihydrotriazine core accommodates within the folate-binding site, while the nature and steric hindrance of the side chains may influence the species-selectivity profile. Structural studies validated the binding hypothesis, as co-crystal structures with *Tb*PTR1 confirmed the predicted ligand orientation and key interactions, whereas co-crystallization attempts with *Tb*DHFR are currently ongoing. These findings support the relevance of the dihydrotriazine core as a promising scaffold for targeting the folate pathway in *T. brucei* parasites and define a comprehensive structure–activity and structure–binding framework for chemical optimization. The improved activity of MTX with our compounds suggests a synergistic mechanism, potentially involving folate pathway modulation and additional targets, warranting further investigation.

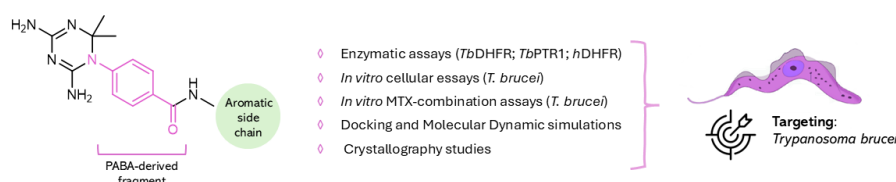


Figure 1. Novel dihydrotriazine series, summary of the studies performed and biological targets.

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OC20

**DISCOVERY OF IRBM-Z-2: A POTENT ALLOSTERIC INHIBITOR OF ZIKA VIRUS NS2B-NS3
PROTEASE WITH ORAL EFFICACY IN MOUSE MODELS**

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Flaviviruses, including Zika, Dengue, West Nile, and Yellow Fever viruses, represent a major global health threat. Zika virus, in particular, has caused alarm due to its rapid spread and severe complications, such as congenital Zika syndrome and Guillain-Barré syndrome. Currently, management relies solely on supportive care, as no approved antiviral drugs or vaccines are available.

Here, we report the discovery of a novel series of *N*-acylsydnone imine-based compounds that act as allosteric inhibitors, blocking Zika virus replication by stabilizing the NS2B-NS3 protease in an inactive conformation.^[1] Employing a stable ZIKV replicon-based cellular phenotypic high-throughput screening assay, we identified the initial hit IRBM-Z-1. Resistance mapping pinpointed the viral NS2B-NS3 protease as the primary target, a finding validated through enzymatic assays and crystallographic structural studies. A structure-guided optimization^[2] effort subsequently yielded IRBM-Z-2, a potent inhibitor exhibiting low-nanomolar activity in both viral replication and anti-infectivity assays, along with a promising preclinical profile and robust efficacy in a mouse model of infection. Notably, IRBM-Z-2 also inhibits proteases from other *Flaviviridae* members, highlighting the broader potential of allosteric protease inhibitors as components of pandemic preparedness strategies.

This study provides proof-of-concept for the *in vivo* therapeutic efficacy of Zika virus protease inhibitors and illustrates how the integration of phenotypic screening, resistance mapping, enzymology, and medicinal chemistry can accelerate the discovery of antivirals against Zika virus and related flaviviruses.

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OC21

2-AROYL-5,6-DIMETHOXYBENZOFURANS AND DEMETHYLATED DERIVATIVES AS NOVEL THERAPEUTIC TOOLS AGAINST GLIOBLASTOMA

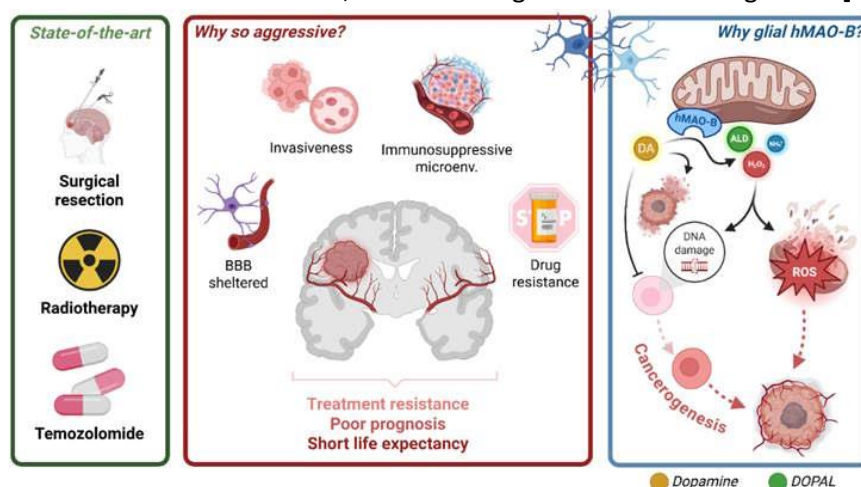
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Glioblastoma is the most aggressive malignant brain tumour, with a dramatically low life expectancy. The therapeutic options are currently limited to surgical resection, radiotherapy and treatment with temozolomide (TMZ), whose efficacy is limited by numerous resistance mechanisms and TMZ' severe adverse effects [1]. High levels of human monoamine oxidase B (hMAO-B), a flavin enzyme deputed to the catabolism of monoamines, are found in glioblastoma cells and it is involved in the production of ROS and other toxic species. The inhibition of hMAO-B would result in a decrease in ROS levels and would hinder the degeneration of cells into a cancerous state (see **Figure 1**). On the other hand, in glioblastoma cells, the hMAO-B inhibition would exert an anticancer effect through the local increase in dopamine concentration, which would cause an increase in the antitumoral immune response, inhibit pro-inflammatory pathways, angiogenesis, tumour growth and cancer proliferation. Moreover, increased dopamine levels seem to increase the efficacy of temozolomide treatment, hence causing a chemosensitizing effect [2].



For these reasons, we have synthesized and preliminarily characterized novel selective hMAO-B inhibitors based on the 2-aryl-5,6-dimethoxybenzofuran scaffold as potential therapeutics for glioblastoma. Furthermore, the demethylation of the methoxyl groups has brought to 5,6-dihydroxybenzofurans, whose catechol-like structure is able to chelate ferrous iron and hence limit its role in cancer development [3]. These two series of compounds have been tested *in vitro* and have shown to have an interesting profile, with notable hMAO-B inhibitory activity and ferrous iron chelating ability. These preliminary findings suggest a promising activity by these compounds and the potential to widen the clinical tools against glioblastoma.

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OC22

EXPLOITING HO-1 INHIBITION THROUGH MUTUAL PRODRUGS STRATEGY FOR IMPROVING 5-FLUOROURACIL EFFICACY

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Targeting the heme oxygenase-1 (HO-1) has emerged as a promising strategy to sensitize tumor cells to chemotherapy, as its overexpression in cancer is associated with tumor progression, angiogenesis, immune evasion, and resistance to therapy [1,2]. In this study, we synthesized novel azole-based HO-1 inhibitors (HO-1i) with the aim of optimizing their drug-like profile. To this end, a new series was developed by replacing the imidazole moiety with a 1,2,4-triazole scaffold as the heme-coordinating group, while preserving the binding mode confirmed by molecular docking. Among the synthesized compounds, LS 8/66 emerged as a promising candidate. *In vitro* HO-1 inhibition and ADMET profiling revealed that it retained high inhibitory activity while achieving a 10-fold improvement in aqueous solubility compared to its imidazole analogue (LS 6/42), along with improved logD values and a better safety profile toward hERG channels. Based on these results, LS 8/66 was selected for the development of novel mutual prodrugs with 5-fluorouracil (5-FU), a well-established anticancer agent. The HO-1 inhibitor was conjugated to the hydroxymethyl-5-FU moiety through cleavable linkers such as succinic and glutaric acid, yielding the mutual prodrugs SI 3/02 and SI 3/08, respectively. Alternatively, to enhance chemical stability, 5-fluorouracil-1-yl acetic acid was used as the 5-FU moiety, affording the mutual prodrug SI 3/07. All mutual prodrugs exhibited high chemical stability in PBS and SGF ($t_{1/2} > 48$ h) and good stability in human plasma ($t_{1/2} = 13$ –21 h), thus preventing premature drug release prior to reaching the target site. Following screening across a panel of cancer cell lines overexpressing HO-1, antiproliferative assays were conducted on MCF-7 breast cancer cells, demonstrating that SI 3/02 displayed the most potent activity, outperforming 5-FU alone and showing efficacy comparable to the co-administration of the parent drugs at a dose of 10 μ M. Also, SI 3/02 showed the ability to inhibit the HO activity in MCF-7 cells, although with lower potency than the parent compound LS 8/66. Given the pro-tumorigenic role of mammary adipose-derived mesenchymal stem cells (Ad-MSCs) in breast cancer, the impact of SI 3/02 on MCF7 was also investigated in co-culture with adipose cells by employing a 3D model. Results showed that SI 3/02 affects stem-like properties of cancer cells by significantly reducing both size and viability of MCF7-Ad-MSCs spheroids, thus supporting the translational potential of these findings.

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OC23

IMPROVING THE KNOWLEDGE OF HUMAN MICROBIOTA: PRODUCTION, CHARACTERIZATION AND MODULATION OF NOVEL CARBONIC ANHYDRASES FROM PROBIOTIC BACTERIAPaoletti N.^a, Carradori S.^b, De Luca V.^c, Bonardi A.^a, Gratteri P.^a, Supuran C.T.^a, Capasso C.^c^aNEUROFARBA Department, Section of Pharmaceutical and Nutraceutical Sciences, University of Florence, Polo Scientifico, Via U. Schiff 6, 50019, Sesto Fiorentino, Firenze, Italy^bDepartment of Pharmacy, "G. d'Annunzio" University of Chieti-Pescara, via dei Vestini 31, 66100, Chieti, Italy^cDepartment of Biology, Agriculture and Food Sciences, CNR, Institute of Biosciences and Bioresources, Napoli, 80131, Italy
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The human gut microbiota plays a crucial role in maintaining host health, and its enzymatic machinery represents a promising yet underexplored source of therapeutic targets. In this study, we report the production, functional characterization, and modulation of three carbonic anhydrases (CAs) derived from key probiotic species: *Segatella copri* (ScoCA β), *Akkermansia muciniphila* (AmuCA γ), and *Faecalibacterium prausnitzii* (FprCA γ). These enzymes, belonging to β - and γ -CA classes, were successfully expressed as recombinant proteins and obtained in soluble, catalytically active forms.

Kinetic analyses demonstrated that all three enzymes are efficient catalysts of CO₂ hydration, with γ -class enzymes showing higher activity than ScoCA β , although remaining less efficient than the highly active human CA II. Inhibition studies performed using a broad panel of inorganic anions and sulfonamide-based compounds revealed distinct and enzyme-specific inhibition profiles. In particular, ScoCA β exhibited limited sensitivity to most inhibitors, whereas AmuCA γ and FprCA γ displayed moderate and selective susceptibility, highlighting significant differences from both human α -class CAs and pathogenic bacterial enzymes.

Complementary activation studies with amino acids and amines further emphasized the functional diversity of these enzymes. AmuCA γ emerged as the most responsive isoform, while ScoCA β showed a more restricted activation pattern. Notably, selected activators exhibited preferential activity toward probiotic enzymes over pathogenic counterparts, suggesting the possibility of selectively modulating microbiota-associated CAs.

In silico modeling and docking studies provided structural insights into enzyme–ligand interactions, confirming the key role of active-site architecture in determining both inhibition and activation profiles. Differences in hydrogen bonding networks, steric constraints, and residue composition were found to underlie the observed selectivity.

Overall, this work highlights the distinctive modulation landscape of probiotic-derived carbonic anhydrases and supports their potential as selective targets for therapeutic strategies aimed at modulating gut microbiota without disrupting beneficial bacterial populations.



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OC24

BEYOND THE G-QUADRUPLEX: STRUCTURE-BASED VIRTUAL SCREENING OF THE HIV-1 LTR-III ARCHITECTURE IDENTIFIES NOVEL ANTIVIRAL LIGANDS

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The Long Terminal Repeat III (LTR-III) region of HIV-1 represents an attractive antiviral target due to its ability to fold into a complex and highly structured nucleic acid architecture involved in the regulation of viral transcription. Structural studies have revealed that LTR-III is composed of three distinct and functionally interconnected elements¹: a canonical G-quadruplex (G4) core, a junction region linking different secondary structure motifs, and a stem-loop domain. The coexistence of these structural features offers multiple opportunities for selective ligand recognition and modulation of viral gene expression.

In this study, we implemented an integrated structure-based virtual screening campaign aimed at identifying novel small molecules capable of targeting the LTR-III structure. Rather than focusing exclusively on the G4 core, independent computational screening workflows were developed for each of the three structural domains, the G-quadruplex, the junction region, and the stem-loop motif, to explore distinct binding pockets and interaction patterns. Large and chemically diverse virtual libraries were screened using molecular docking and post-docking filtering procedures², allowing the identification of compounds predicted to selectively recognize individual structural elements or simultaneously engage multiple regions of the LTR-III architecture.

The resulting hit compounds represent novel chemical scaffolds with potential antiviral activity through the stabilization or modulation of the LTR-III structure, ultimately affecting HIV-1 transcriptional regulation. Preliminary biophysical investigations provided initial support for the computational findings, indicating that selected compounds are able to interact with the LTR-III architecture. Moreover, early biological evaluations suggest that some of the identified hits may possess antiviral potential, warranting further investigation of their mechanism of action and therapeutic relevance. This multi-target structural approach expands the current paradigm of G4-directed antiviral discovery and highlights the importance of considering the full structural complexity of regulatory nucleic acid elements to identify innovative therapeutic candidates against HIV-1.

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OC25

EXPANDING THE HORIZON OF LABEL-FREE CTC DETECTION: TOWARD A CXCR4-TARGETED PLASMONIC OPTICAL FIBER BIOSENSOR FOR LIQUID BIOPSY APPLICATIONS

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The detection of Circulating Tumor Cells (CTCs) is a critical challenge in liquid biopsy, requiring analytical platforms that combine high sensitivity with stringent selectivity^[1]. Among key cancer biomarkers, the C-X-C chemokine receptor 4 (CXCR4) plays a pivotal role in tumor progression and dissemination^[2], yet its label-free monitoring for CTC detection remains underdeveloped. Here, we report a highly sensitive Surface Plasmon Resonance (SPR) optical fiber biosensing platform^[3] functionalized with a novel CXCR4-antagonist peptide (Peptide 5) whose high binding affinity ($IC_{50} = 2.4 \pm 1.0$ nM) ensures selective cell capture at the sensing interface. The sensor demonstrates the ability to discriminate CXCR4-overexpressing cells from non-target populations, achieving a limit of detection at the single-cell level (1 cell/20 μ L). Notably, this sensitivity is maintained even in the presence of a 50-fold excess of peripheral blood mononuclear cells (PBMCs), where the binding event produces a characteristic resonance blue shift. This Point-of-Care Test provides a mechanistically validated signature for the recognition of malignant phenotypes in complex environments. This study establishes a robust foundation for the development of CXCR4-targeted photonic diagnostics, paving the way for next-generation liquid biopsy applications to monitor tumor evolution and therapeutic efficacy in real-time.



Figure 1. Schematic illustration of the SPR-POF platform functionalization and target cell capture principle.

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OC26

RATIONAL DESIGN, SYNTHESIS AND STRUCTURAL MECHANISM OF MSP20, A NOVEL TRPV1 AGONIST ENDOWED WITH LONG-LASTING ANALGESIC ACTION

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Transient receptor potential vanilloid type-1 (TRPV1) is a polymodal receptor involved in pain perception and neuronal signalling, representing an attractive target for the development of addiction-free analgesics and neuroprotective agents. Building on our previous studies on thiophene-based TRPV1 agonists and leveraging an *in silico*-guided rational drug design strategy (figure 1), we designed, synthesized, and characterized a new class of benzothiophene-substituted TRPV1 agonists displaying high affinity and efficacy toward the receptor. [1]

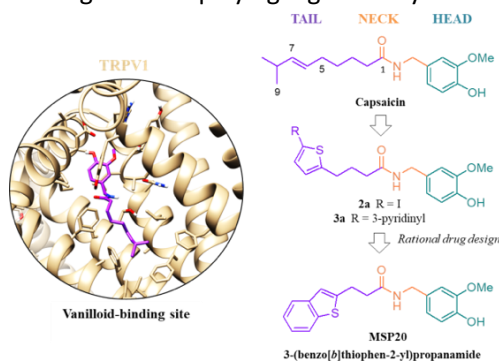


Figure 1. Chemical features of capsaicin and synthesized amide derivatives targeting TRPV1.

In vitro functional studies demonstrated that prolonged or repeated exposure to these compounds induced calcium-dependent TRPV1 desensitization, rendering the channel insensitive to noxious stimuli. To elucidate the molecular basis of this effect, we solved a cryo-electron microscopy (cryo-EM) structure of human TRPV1 (*h*TRPV1) in complex with the most promising agonist, MSP20. The structure reveals the molecular determinants of MSP20 binding within the vanilloid pocket and captures *h*TRPV1 in a desensitized conformation characterized by a closed ion channel pore, an α -helical C-terminus, and distinct annular lipid organization. Importantly, *in vivo* experiments demonstrated that MSP20 exerts robust and long-lasting antinociceptive activity, together with *ex vivo* neuroprotective effects. Overall, these findings support benzothiophene-substituted vanilloids as promising candidates for the development of next-generation analgesic agents.

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OC27

EXPLORING LIGANDABLE POCKETS OF 3D OncoPPI NETWORKS FOR IMPROVING PROTEIN INHIBITION AND DEGRADATION STRATEGIES

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The understanding of protein-protein interaction (PPI) networks is extremely important to unveil the rationale behind the onset of cancers and of its different disease phenotypes. Identifying oncogenic proteins causatively related to specific cancer types is thus essential for designing customizable therapeutic approaches, based either on small-molecule inhibitors or targeted protein degradation strategies that selectively remove disease-related proteins through cellular degradation pathways [1,2].

In this work, we propose a flexible and systematic framework focusing on PPIs involved in 12 different cancer types (oncoPPIs), aiming to scan protein pockets that serve as recognition sites for modulating protein function [3]. First, we constructed a comprehensive pocketome based on 314 solved oncoPPIs to map all the putative ligandable protein pockets through geometric and energetic 3D GRID-MIFs descriptors (Figure 1).

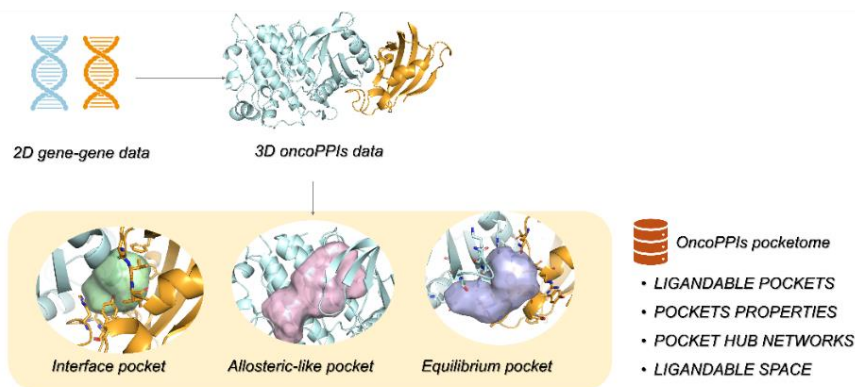


Figure 1. Classification of ligandable pockets mapped onto solved 3D oncoPPI structures.

Next, the pockets were classified according to their complementarity towards oncoPPI inhibitors or PROTACs. Ligand-bound pockets retrieved from solved crystal structures were then investigated to assess the differences across cancer types. Finally, 3D oncoPPI networks were generated for each cancer type to identify the most connected and central proteins (i.e., hubs), enabling not only the identification of key cancer-associated proteins but also the characterization of pockets and residues involved in critical and potentially druggable interactions. All data are freely available at <https://github.com/molDiscovery/OncoPPI-pocketome> repository, paving the way for improving protein inhibition and degradation approaches in a more informed cancer research.

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OC28

UPCYCLING SPINACH PROCESSING BY-PRODUCTS INTO HIGH-VALUE BIOACTIVES: GREEN EXTRACTION OPTIMIZATION AND IN VIVO PHOTOPROTECTIVE ACTIVITY IN ZEBRAFISH MODELS

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The global market for functional foods and dietary supplements is rapidly expanding, driven by increasing consumer demand for safe, natural, and high-value nutritional products [1]. The recovery of bioactive substances from plant-based side streams is central to environmental sustainability and the circular bioeconomy, directly contributing to the United Nations 2030 Agenda, particularly SDGs 9, 12 and 13 [2]. Within this framework, the valorization of spinach-derived agri-food residues (*Spinacia oleracea* L.), specifically discarded cotyledons from the fresh-cut vegetable industry, represents a strategic opportunity to recover high-value molecules that are often more concentrated in these by-products than in the corresponding retail products.

In this study, a sustainable valorization strategy was developed using Microwave-Assisted Extraction (MAE). A preliminary green defatting step using cyclopentyl methyl ether (CPME) was implemented to selectively remove chlorophylls and fatty acids. To maximize efficiency, a Box–Behnken design (BBD) was employed to optimize three independent variables: ethanol concentration (0–100%), extraction time (5–35 min), and temperature (60–100 °C). The evaluated responses included total phenolic, flavonoid, tannin, and saponin contents, alongside multiple antioxidant assays (DPPH, ABTS, ORAC, FRAP).

Statistical analysis confirmed the robustness of the models, with a non-significant “lack of fit”. 3D response surface analysis identified a synergistic interaction between extraction time and ethanol concentration, while temperature above specific thresholds negatively affected the responses. Multi-response optimization identified the optimal extraction condition as 21.04% ethanol, 29.16 min, and 73.58 °C.

Under these validated conditions, phytochemical characterization via UHPLC-HRMS/MS led to the putative annotation of 53 compounds, predominantly patuletin and spinacetin derivatives, phenolic acids, and oleanane-type saponins. A semi-quantitative method was validated according to FDA Bioanalytical Method Validation Guidance, showing good precision and accuracy [3]. Finally, multivariate analysis (PCA and HCA) demonstrated that the optimized hydroethanolic system provides the most comprehensive chemical profile, effectively covering both polar and less polar metabolites.

To evaluate the biological activity of the optimized phytocomplex, its protective effects were investigated in an *in vitro* UVA-induced oxidative stress model in HaCaT cells, in which the extract showed protective antioxidant effects. These findings were further confirmed in an *in vivo* zebrafish model exposed to UVA irradiation. In addition, the extract significantly reduced melanin accumulation and inhibited tyrosinase activity in zebrafish larvae, effects that were corroborated by complementary enzymatic tyrosinase assay. In conclusion, this research establishes a scalable and sustainable framework for transforming low-cost spinach residues into high-value functional ingredients for applications in the food, nutraceutical, and cosmeceutical industries, thereby supporting the transition toward a circular bioeconomy models.

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OC29

DESIGNING DUAL-ACTION LUMINESCENT INHIBITORS OF TYROSINASE: SYNTHESIS AND BIOLOGICAL EVALUATION

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Tyrosinase (TYR, EC 1.14.18.1) is a copper-containing metalloenzyme involved in melanin biosynthesis, where it catalyses the hydroxylation of L-Tyrosine to L-Dopa and the oxidation of L-Dopa to Dopaoquinone [1]. TYR overexpression is frequently associated with melanoma progression and hyperpigmentation disorders, making this enzyme an attractive target for diagnostic and therapeutic applications. Consequently, the bioimaging-based detection of TYR plays a pivotal role in elucidating its mechanisms of action and improving early clinical diagnosis [2]. Beyond detection, the development of compounds inhibiting TYR activity opens promising avenues for the design of dual-action agents, which concurrently track and treat pathological conditions driven by aberrant melanin accumulation.

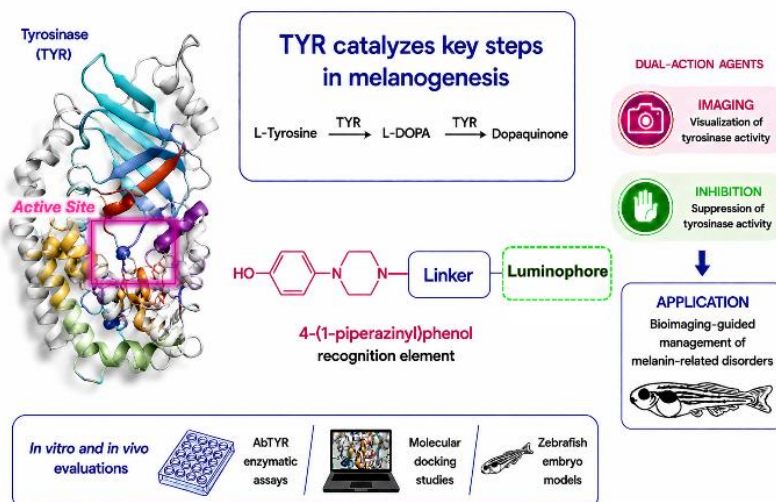


Figure 1.

This study reports the design and synthesis of a focused library of luminescent 4-(1-piperazinyl)phenol derivatives, incorporating BODIPY or curcumin scaffolds to target the TYR monophenolase and diphenolase activities (Figure 1) [3,4]. Through a comprehensive, multi-layered evaluation, spanning *in vitro* AbTYR assays, molecular docking, and *in vivo* zebrafish embryo models, several compounds emerge as potent multifunctional agents, for bioimaging-guided therapy of melanin-related disorders.

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OC30

STRUCTURAL DETERMINANTS GOVERNING LIGAND-BINDING DOMAIN OPENING OF THE DAF-12 RECEPTOR

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The nuclear receptor DAF-12 functions as a key molecular switch controlling the nematode life cycle.[1,2] Its activation, triggered by binding to the endogenous steroidal ligand 25(S)- Δ^7 -dafachronic acid (DA) (1) (**Figure 1**), regulates gene expression programs that are critical for development and reproductive maturation. An expanding body of evidence highlights the role of DAF-12 signaling as a developmental regulator in the infective processes of various parasitic nematodes, including *Strongyloides stercoralis*. [3] In this communication, we present our ongoing efforts to elucidate the molecular mechanisms and structural features underlying DAF-12 signaling modulation.[4,5] Specifically, we have synthesized a series of novel DA derivatives modified at the terminal carboxylic group to assess their influence on receptor activation and on the opening mechanism of the ligand-binding domain (LBD). These compounds were evaluated for their ability to modulate DAF-12 activity and were further examined through structure–activity relationship (SAR) analyses using a deep learning based docking method combined with molecular dynamics simulations (**Figure 1**). Overall, our findings provide new insights into the SAR of DA derivatives as DAF-12 ligands and identify key structural elements governing their activity, thereby supporting the development of effective therapeutic strategies against parasitic infections.

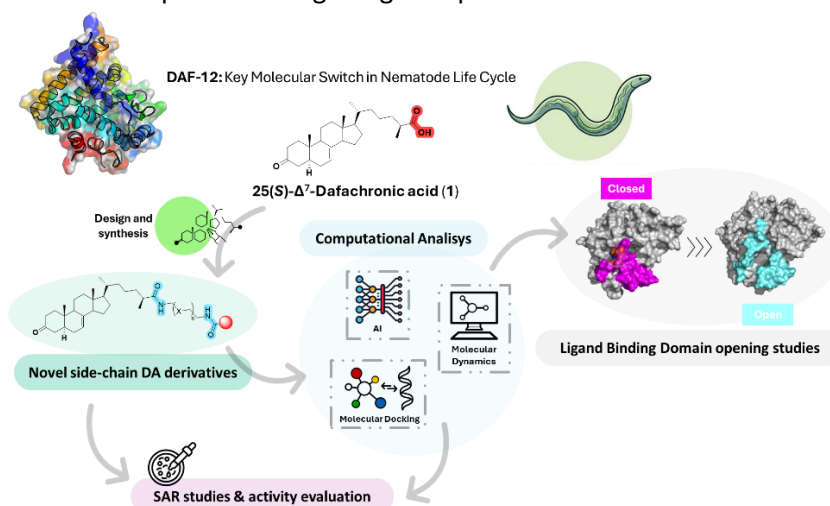


Figure 1. Overview of the work-flow followed in this work.

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FLASH COMMUNICATIONS

FC01

HISTONE DEACETYLASE 6 AT THE CROSSROADS OF CANCER AND INFECTIOUS DISEASES

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Histone deacetylase 6 (HDAC6) is a unique member of HDAC family, predominantly localized in cell cytoplasm and targeting a wide range of non-histone proteins, including cortactin, α -tubulin, Hsp90, and ubiquitin, thereby playing a key role in maintaining cellular homeostasis. Accordingly, dysregulated HDAC6 activity has been found to drive multiple oncogenic pathways, by promoting aberrant cell proliferation and differentiation, cell-death pathways, and epithelial-to-mesenchymal transition, and liquid-liquid phase separation, all of which contributing to tumor progression and metastatic dissemination [1]. Moreover, HDAC6 is a critical regulator of immune response, by modulating the production of inflammatory markers, thereby shaping cellular response to infective agents. In light of the current lack of clinically approved selective HDAC6 inhibitors, we aimed to reshape HDAC-targeted therapies by identifying *1,3,8-triazaspiro[4,5]decan-4-one core* as a suitable motif for the preferential binding with HDAC6 over nuclear isoforms. Through appropriate decoration of this *capping moiety*, we identified a promising preclinical candidate, namely **Mesinostat** (named after **M**argherita, **E**lisabetta, **S**imona, and **I**vana with the familiar '*nostat*' suffix, commonly used for HDAC inhibitors; IC₅₀ HDAC6 = 7.7 nM, IC₅₀ HDAC1 = 2188 nM; Selectivity index HDAC1/HDAC6 = 275) which showed efficacy in patient-derived triple negative breast cancer organoids, reducing cancer cells stemness, and inducing cell death through the activation both pro-apoptotic and pro-autophagic pathways [2,3]. In a second design, prompted by our previous results for the efficacy of HDAC6 pharmacological inhibition in a murine model of *P. aeruginosa* infection [4], coupled by the evidence that bacteria and fungi express HDAC-like enzymes involved in chemoresistance, biofilm formation and virulence factor production, we further investigated the impact of proprietary HDAC6 inhibitors in modulating both bacteria and fungi virulence. We identified compound **F2F-202** (IC₅₀ HDAC6 = 7.1 nM; IC₅₀ HDAC1 = 2191 nM, Selectivity Index = 422) as a novel high potent and selective HDAC6 inhibitor able to target fungal HDA1 and bacterial PA3774 (both structurally related to human HDACs), thereby inhibiting the production of virulence factors of *P. aeruginosa* and *C. albicans* clinical isolates, accompanied by reduced biofilm formation [5, 6]. To improve PK properties of such class of compounds, heteroaryl zinc-binding groups were coupled with spirofused capping moieties, yielding a novel class of selective, tight- and slow-binding HDAC6 inhibitors [7]. Collectively, our findings support the further development of selective HDAC6 inhibitors for the identification of next-generation therapeutic options to treat major public health challenges, reinforcing the multifactorial role of HDAC6 in regulating diverse physio-pathological states.

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FC02

EXPLORATION OF THIAZOLE-BASED SCAFFOLDS FOR THE DEVELOPMENT OF BROAD-SPECTRUM ANTIVIRAL AGENTS

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Thiazoles and thiazolo[5,4-*b*]pyridine systems are recognized as privileged scaffolds in antiviral drug discovery, thus representing promising starting points for the development of new antiviral agents against respiratory viruses [1,2]. Among viral targets, SARS-CoV-2 Nsp13 helicase has emerged as an attractive druggable target for the identification of broad-spectrum antiviral agents against resistant viral strains. Based on computational studies of the Nsp13-Z2327226104 complex (PDB ID: 7NNG) [3], combined with MM/GBSA analyses and QikProp properties predictions, we designed and synthesized two series of [1,3]thiazolo[5,4-*b*]pyridine (**1**) and [1,3]thiazolo[5,4-*h*][1,6]naphthyridine (**2**) derivatives (Figure 1). Biochemical assays on SARS-CoV-2 Nsp13 helicase identified several derivatives displaying inhibitory activity in the micromolar range, by competing with ATP for its binding site. Cell-based assays against a panel of viruses, led to the identification of a naphthyridine derivative with remarkable antiviral activity against human coronavirus HCoV-229E (EC_{50} = 0.85 μ M), thus emerging as a promising lead compound for further optimization.

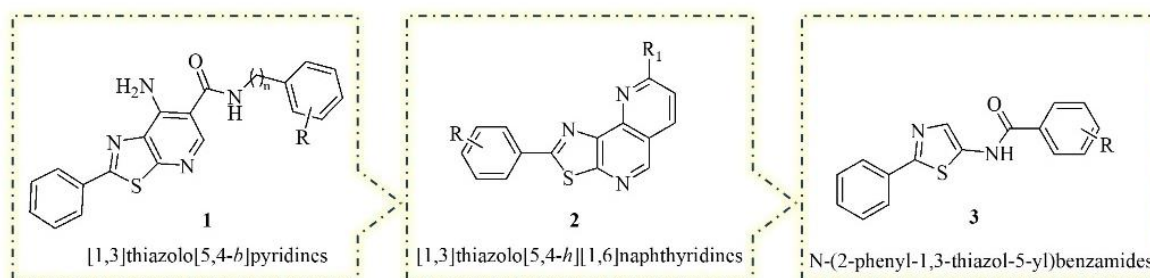


Figure 1. Thiazole-based derivatives 1-3.

To further explore the versatility of the thiazole core, a *scaffold hopping* strategy was applied to obtain a series of *N*-(2-phenyl-1,3-thiazol-5-yl)benzamides (**3**). Several compounds showed potent and selective activity against multiple Influenza A/H1N1 strains, with submicromolar to low micromolar EC_{50} values (0.04-1.80 μ M). Mechanistic studies supported by pseudovirus entry assays in MDCK cells confirmed inhibition of the H1N1 HA-mediated viral entry process. Overall, these findings highlight the potential for developing new, potent and selective antiviral agents based on the designed thiazole framework.

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FC03

LUMINAL A BREAST CANCER SECRETOME DRIVES *ENTEROCOCCUS FAECALIS* TOWARD AN ONCO-VIRULENCE PHENOTYPEAl-Ansari M.¹, Mahmood S.¹, Alwan M.²¹ Department of Botany and Microbiology, College of Science, King Saud University,
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The breast tumor microenvironment (TME) actively modulates the behavior of resident microbiota, yet the specific mechanisms by which the luminal A breast cancer secretome influences bacterial pathogenicity remain poorly understood. This study investigated the capacity of MCF-7-derived paracrine factors to reprogram the phenotypic and genotypic profile of *Enterococcus faecalis*, an opportunistic pathogen frequently associated with breast tissue dysbiosis. To assess this, *E. faecalis* was cultured in serum-free conditioned media (CM) harvested from MCF-7 cells, with MCF-10A non-tumorigenic cells and cell-free basal media serving as comparative controls. The impact of the secretome was evaluated through a multi-parametric approach encompassing 72-hour growth kinetics, scanning electron microscopy (SEM) for structural analysis, biofilm quantification, antimicrobial susceptibility testing, and semi-solid agar chemotaxis assays, alongside qPCR-based expression profiling of virulence determinants. While exposure to the MCF-7 secretome did not significantly alter microbial proliferation or chemotaxis, it induced marked, dose-dependent morphological aberrations including membrane roughening, cellular blebbing, deformation, and extensive cell aggregation indicative of a significant structural response to the malignant secretome. These modifications were accompanied by significant shifts in biofilm architecture and selective alterations in antimicrobial resistance profiles. Crucially, molecular profiling revealed a significant upregulation of the virulence-associated genes *fsrC* and *esp*, signaling a definitive transition toward an enhanced pathogenic state. These findings demonstrate that secretomes derived from luminal A breast cancer cells actively reprogram the structural integrity and transcriptomic virulence profile of *E. faecalis* independent of mitogenic effects, establishing a novel "onco-virulence" axis wherein tumor-derived factors function as direct modulators of bacterial pathogenicity within the breast TME.

Keywords: luminal A breast cancer, *Enterococcus faecalis*, tumor secretome, onco-virulence, virulence genes, ultrastructural remodeling

FC04

DESIGN AND SYNTHESIS OF SMALL MOLECULES AS MICRORNA MODULATORS IN ISCHEMIC STROKE

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MicroRNAs are involved in various diseases, and recent studies indicate that they can be targeted by molecules. Their therapeutic use and the choice of using them mainly comes from the ability to regulate multiple targets at the same time. Their expression varies and may be indicative of a disease. Certain microRNAs are altered in conditions such as thrombosis, angiogenesis, neuroinflammation and, they are strongly linked to ischemic stroke. In this study a series of small molecules were designed and synthesized as potential miRNA ligands. The design results from the combination of structural elements capable of interfering with RNA structures and the focus was on miR-150-5p, miR-181b-5p, miR-218-5p and miR-223-5p which are involved in hypoxia, ischaemia and stroke. Through an RNA structure prediction and molecular docking studies it was possible to deepen knowledge on possible interactions and to confirm that the length of these molecules together with the presence of dibenzimidazole are key elements to turning them into excellent binders (**Figure 1**). Subsequently, an activity prediction was carried out to predict the biological activities of the synthesized compounds, and a gene prediction analysis was also conducted to identify target genes directly involved in the onset of ischemic stroke. The compounds were pharmacologically tested by reproducing a real ischemic stroke condition under oxygen and glucose deprivation condition. The compounds were found to be not cytotoxic and cell viability generally remained low, except for three compounds, which increased cell viability at the lowest concentrations. Then, an expression miRNA analysis was conducted in order to understand how miRNAs vary in their expression from a basal condition to a stress condition but also to verify the effects of the tested compounds. This study has thus revealed the potential of these molecules as therapeutic targets, acting as modulators and potential inhibitors of microRNAs, particularly when their upregulation leads to the onset of a disease. In the future, these findings will undoubtedly be further explored to achieve additional improvements and reproduce the studied model *in vivo*.

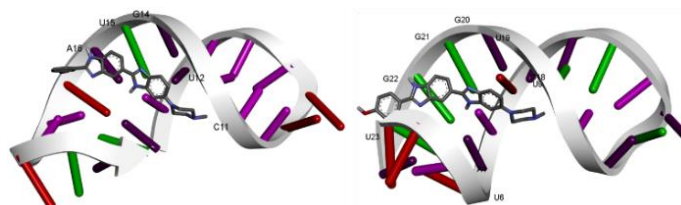


Figure 1. Synthesized compounds in complex with miR-150 and miR-181 structures.

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FC05

DESIGN, SYNTHESIS, AND PHARMACOKINETIC PROFILING OF FLUORINATED REVERSIBLE N-ALKYL CARBAMATE DERIVATIVES OF PSILOCIN FOR SUB-HALLUCINOGENIC BRAIN EXPOSURE

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Psilocybin (PSY), the naturally occurring phosphorylated prodrug of psilocin (PSI), has emerged as a promising therapeutic agent for several neuropsychiatric disorders¹. However, its clinical application remains limited by rapid *in vivo* dephosphorylation to PSI, resulting in high brain exposure and acute hallucinogenic effects². In this study, reversible carbamate-based PSI derivatives were investigated as a strategy to modulate PSI pharmacokinetics and achieve controlled serotonergic signaling within the CNS^{3,4}. Preliminary proof-of-concept studies on *N*-alkyl and amino acid ester-derived carbamates demonstrated that carbamate stability could be finely modulated through structural and electronic tuning of the promoiety. However, extensive ester hydrolysis in several amino acid derivatives generated overly stable carbamates with inefficient *in vivo* PSI release, highlighting the critical importance of balancing carbamate electronic properties to achieve controlled bioreversibility.

To overcome these limitations, a second-generation library of fluorinated *N*-alkyl carbamates was rationally designed. DFT calculations revealed that progressive fluorination increased carbamate NH acidity, strongly correlating with accelerated hydrolysis kinetics under physiological conditions. The synthesized derivatives displayed tunable chemical and plasma stability profiles, enabling systematic modulation of PSI release kinetics. Among them, lead compound 4e exhibited favorable oral bioavailability, efficient blood-brain barrier permeation, and partial bioconversion to PSI, while maintaining significantly lower systemic and central PSI exposure compared with PSY. Notably, 4e induced markedly attenuated head-twitch responses *in vivo* relative to PSY, consistent with reduced hallucinogenic liability. Functional FLIPR-Ca²⁺ assays demonstrated partial agonist activity at 5-HT_{2A} and 5-HT_{2C} receptors, with no detectable activity at 5-HT_{2B}⁴. Collectively, these findings suggest that fluorinated PSI carbamates represent more than simple bioreversible prodrugs, constituting instead a novel class of serotonergic modulators combining intrinsic receptor activity with controlled PSI release. This pharmacological profile supports the development of intrinsically active, non-psychedelic serotonergic derivatives capable of preserving therapeutically relevant neuroplastic effects while minimizing acute psychotropic activity, thereby providing a potential framework for next-generation non-hallucinogenic serotonergic therapeutics. Ongoing studies are focused on the synthesis and pharmacological characterization of chemically stable PSI carbamates specifically designed as non-hallucinogenic serotonergic agents.

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FC06

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL COVALENT INHIBITORS OF MOK KINASE FOR THE TREATMENT OF NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis is a rare, adult-onset neurodegenerative disease characterized by progressive degeneration and loss of motor neurons. Currently there is no cure for ALS and once symptoms arise it is typically lethal within 5 years. Increasing evidence highlights neuroinflammation as a key contributor to ALS progression, with microglia playing a central role in the inflammatory response^[1]. Among the molecular targets involved, MOK (MAPK/MAK/MRK overlapping kinase), a serine/threonine kinase^[2], has recently emerged as a potential mediator of neuroinflammatory pathways in ALS. MOK interacts and colocalizes with cytoplasmic TDP-43 aggregates, a hallmark of ALS pathology. MOK regulates also the function of the epigenetic reader bromodomain- containing protein 4 (Brd4), by supporting its binding to cytokine gene promoters, therefore enabling innate immune responses^{[3][4]}. MOK is one of the only two human kinases with an endogenous cysteine gatekeeper residue, making it an attractive target for covalent inhibition^[5]. Starting from the compounds previously reported in the literature, we designed and successfully synthesized a library of derivatives aimed at improving non-covalent interactions and the overall target affinity. Computational studies, including covalent docking simulation, were performed to evaluate ligand-protein binding and to help us to select the best compounds to synthesize. Anti-inflammatory properties of the synthesized compounds were then evaluated in vitro on murine SIM-A9 microglial cells stimulated with LPS to induce the inflammatory response. Wild-Type and MOK-knockout SIMA9 cells were both used to evaluate the selectivity towards MOK. The production of pro-inflammatory cytokines was quantified by ELISA, and cytotoxicity was assessed using MTT assay.

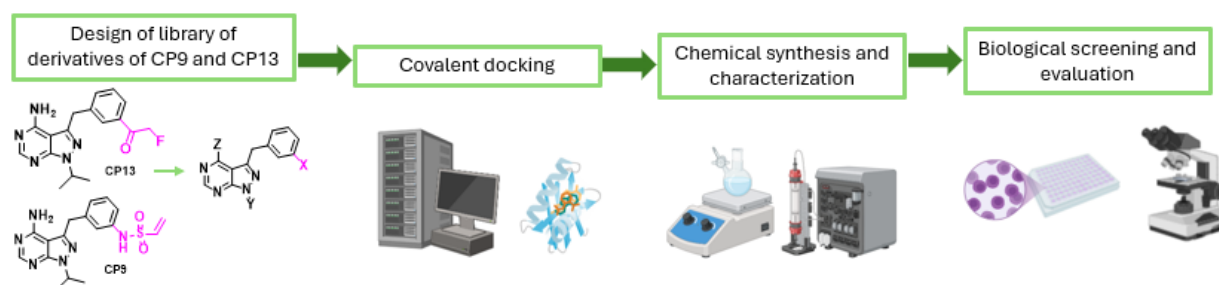


Figure 1

References:

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FC07

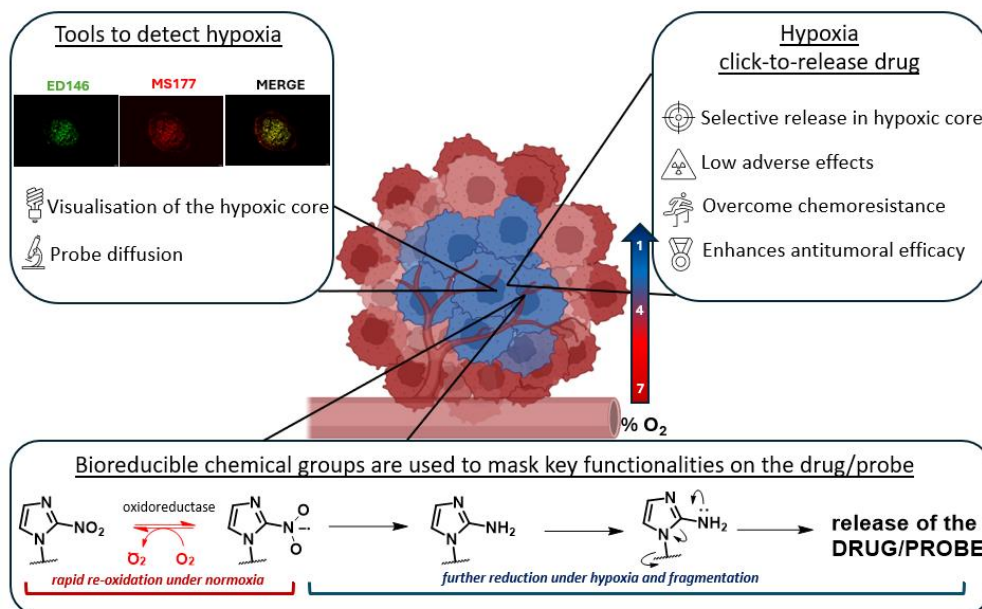
CLICK CHEMISTRY-BASED STRATEGIES FOR HYPOXIA IMAGING AND TARGETED DRUG DELIVERY IN COLORECTAL CANCER MODELS

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Hypoxia is a well-established hallmark of solid tumors, closely linked to poor clinical outcomes, enhanced tumor aggressiveness, and reduced sensitivity to chemo- and radiotherapy. Arising from the uncontrolled proliferation and elevated metabolic activity of cancer cells, oxygen-deficient regions develop predominantly within the tumor core. The spatio-temporal heterogeneity of tumor hypoxia, ranging from moderate (~4% O₂) to severe (<0.5% O₂) oxygen levels, poses significant obstacles for drug penetration and precise characterization of the tumor microenvironment.¹

In our ongoing interest in tumor hypoxia², the present project explores the use of biorthogonal click chemistry with a dual mean (Figure 1): (i) to develop clickable fluorescent probes specifically designed to detect and image hypoxic areas and (ii) to release chemotherapeutic agents which are still employed as first-line therapies in the metastatic setting of colorectal cancer. Both approaches are based on the use of bioreductive masking groups which are reduced and fragmented when the oxygen levels are low. On one hand, the ability to identify and visualize hypoxic tumour regions at a certain time of the therapeutic regimens is essential for determine which patients would benefit most from conventional chemo- and radiotherapy, and for the rational design of hypoxia-activated prodrugs.³ On the other, the localized release of the active chemotherapeutic agent specifically within the tumour would enhance the therapeutic efficacy while minimizing systemic toxicity.



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FC08

A NEW SERIES OF CARBAZOLE DERIVATIVES WITH ANTI-BREAST CANCER PROPERTIES

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Carbazoles are a key class of heterocyclic compounds in medicinal chemistry, widely studied for their many biological properties, including antibacterial, antimalarial, antioxidant, antidiabetic, neuroprotective, anticancer and many more (Figure 1) [1]. Recently, this scaffold has gained significant attention for its activity against breast cancer, which remains the most common cancer in women and a major health concern despite ongoing research [2]. Given the complexity of this disease, the toxicity of standard treatments and the risk of drug resistance, there is an urgent need for new and effective anti-breast cancer agents with better pharmaceutical profiles [3]. In this study, we evaluated the cytotoxic potential of a novel library of carbazole derivatives against a panel of human breast cancer cell lines (MDA-MB-231, MDA-MB-453 and MCF-7). Our findings identified compound **6** as the lead candidate, exhibiting high efficacy against triple-negative breast cancer (TNBC), specifically the MDA-MB-231 and MDA-MB-453 cell lines (IC₅₀ values equal to 0.45±0.01 and 0.65±0.02 μM, respectively), which are the most aggressive and metastatic. Furthermore, they did not interfere with the growth of the normal cell line MCF-10A, contrarily to Ellipticine, a well-known carbazole derivative, used as a reference molecule. Further investigations revealed that compound **6** acted as inhibitor of actin polymerization and reduced cell migration, interfering with some key molecular markers associated with epithelial-mesenchymal transition (EMT), invasion and metastasis. In conclusion, compound **6** emerged as a promising lead for the development of targeted therapeutic strategies against metastatic TNBC.

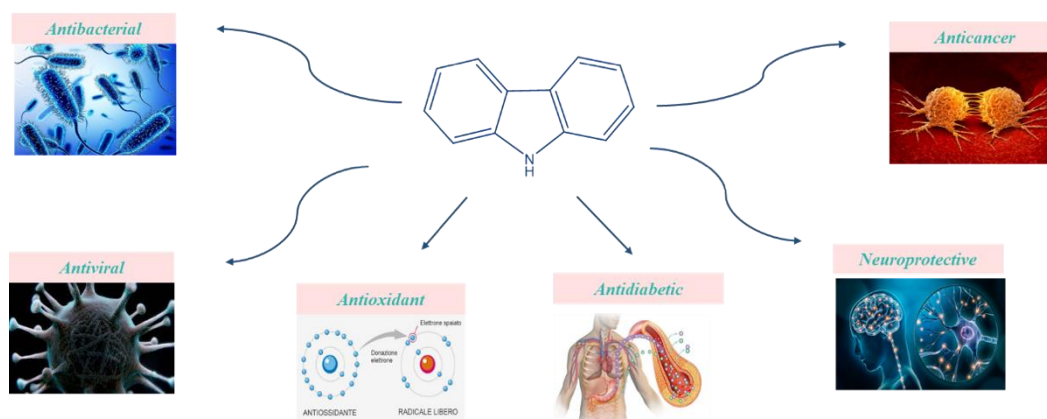


Figure 1. Carbazole scaffold in medicinal chemistry.

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FC09

STEREOSPECIFICITY MEMBRANE IMPACT OF TWO CATECHINS ON RED BLOOD CELLS

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Catechins are flavanols characterized by a basic structure consisting of two benzene rings and a hydropyran heterocyclic ring [1]. In (-)-epicatechin (ECT), the substituents at C2 and C3 of the dihydropyran ring are in *cis* configuration, whereas in (+)-catechin (CT), they are in *trans* configuration [2]. Catechins tend to interact with membrane proteins, affecting their activity and/or function and metabolic processes [2]. In this study, the impact of CT and ECT on erythrocyte membrane and cell functions was analyzed. Surprisingly, although the two compounds have a very similar structure and differ only in the orientation of the hydroxyl group in C3, they exert opposite effects on $\text{HCO}_3^-/\text{Cl}^-$ exchange mediated by band 3 protein (AE1) in red blood cells. Specifically, anion transport is reduced in the presence of CT compared with ECT, which conversely increases it, and this observation aligns with the mechanisms of action we hypothesized *in silico* for the two compounds. Molecular mechanism simulations suggest that ECT enhances HCO_3^- binding affinity, mainly through the formation of a H-bond between its C3-OH and HCO_3^- that stabilizes the anion within its binding site. In contrast, CT occupies the anion binding site through its 5,7-dihydroxyphenyl moiety, thus hindering the anion's access and potentially contributing to a reduction in $\text{HCO}_3^-/\text{Cl}^-$ exchange (Figure 1). These findings could pave the way for further studies aimed at a better understanding of the potential properties and structure–activity relationships of these molecules.

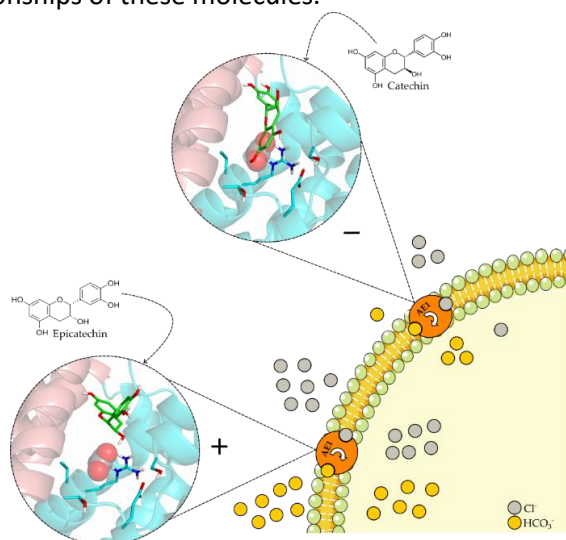


Figure 1. Different mechanisms of action of ECT and CT in AE1 protein.

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XXX

National Meeting on
Medicinal Chemistry

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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

FC10

ADVANCING RNA-TARGETED DRUG DISCOVERY: A BIOPHYSICAL PLATFORM TO IDENTIFY MALAT1 BINDERS AS ANTI-MELANOMA AGENTS

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Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) is a highly conserved, abundantly expressed long non-coding RNA (lncRNA) that modulates gene expression at both transcriptional and post-transcriptional levels.[1] While non-essential for normal development and viability in mice, MALAT1 plays a pivotal role in driving tumor progression and metastasis.[2] Specifically, it is a key regulator of melanoma, an aggressive skin malignancy responsible for over 75% of skin cancer deaths.[3] Interestingly, the 3'-end of MALAT1 contains a stable triple helix structure that prevents its degradation,[4] making this RNA motif a promising target for innovative anticancer therapies. However, small-molecule binders of the MALAT1 triple helix remain largely underexplored, rendering this research area highly attractive and competitive.[5] Here, we developed an integrated platform combining ¹⁹F-NMR, STD-NMR, FRET, and Grating-Coupled Interferometry (GCI) to screen commercially purchased fluorinated fragments and an *in-house* small molecule library as MALAT1 triple helix binders. Identified hits underwent a rigorous validation funnel: binding selectivity towards the triple helix over the MALAT1 hairpin and a general DNA duplex was confirmed via FRET thermal shift assays, while non-specific intercalation was excluded through fluorescent displacement assays. For the top-performing hits, RNase A degradation assays and cellular evaluations confirmed enhanced triple helix degradation and a concomitant decrease in MALAT1 levels. Among the validated hits, a couple of pyrazolobenzothiazine-based small molecules showed the most promising results. Medicinal chemistry efforts were thus focused on this scaffold, leading to the design and synthesis of 30 analogues, which were evaluated for binding affinity, selectivity, and target degradation efficiency. The best pyrazolobenzothiazine derivatives exhibited remarkable cytotoxicity against melanoma cells (A375), with CC₅₀ values in the low micromolar range, demonstrating a promising correlation between cellular phenotypic outcomes and MALAT1 degradation.

In conclusion, this work reports the development of an integrated screening pipeline that led to the discovery and hit optimization of novel MALAT1 small-molecule binders. Furthermore, the established biophysical protocols and screening workflows provide a robust, generalizable framework to accelerate drug discovery targeting other therapeutically relevant RNA structures.

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FC11

SMALL-MOLECULE DEGRADERS FOR ANTIPARASITIC DRUG DISCOVERY AND CHEMICAL BIOLOGY APPLICATIONS

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Leishmaniasis is a vector-borne parasitic disease caused by *Leishmania* spp. Its geographic spread is increasing due to climate change and human mobility, while current therapies remain limited by toxicity, suboptimal efficacy, drug resistance, and poor accessibility. These challenges highlight the need for innovative therapeutic strategies.¹ Targeted Protein Degradation (TPD) is an event-driven pharmacological strategy that offers an alternative to conventional small-molecule inhibitors (**Fig. 1**).² Unlike occupancy-based approaches, TPD relies on small-molecule degraders, including Hydrophobic Tag (HyT) systems, to induce the selective elimination of disease-relevant proteins through activation of the cell's endogenous degradation machinery.³

This project focuses on the design and synthesis of twelve HyT degraders targeting trypanothione reductase (TR), an essential enzyme in the parasite redox metabolism that is absent in the human host. Although TR is a validated target for leishmaniasis, its broad and relatively featureless active site has hindered effective modulation by conventional small molecules.⁴ HyT degraders may overcome this limitation by conjugating a TR-binding ligand to a hydrophobic moiety that mimics misfolded proteins, thereby engaging the parasite protein quality control (PQC) system and promoting selective TR degradation.

A small series of twelve HyTs has been synthesized, using a convergent synthetic strategy to enable structural diversification from a shared intermediate incorporating different linkers and hydrophobic moieties. Preliminary biological evaluation shows promising antiparasitic activity, including intracellular efficacy against amastigote form of the parasite. To investigate the mechanism of action, CRISPR-Cas9 technology has been applied to generate a *L. mexicana* cell line expressing Myc-tagged TR.⁵ This model will enable quantitative assessment of TR levels by Western blot, allowing discrimination between inhibitory and degradation-based effects. Complementary immunoprecipitation studies and pathway inhibition assays will further elucidate involvement of proteasomal and lysosomal systems. Overall, this work explores Hydrophobic Tag-mediated protein degradation as a new strategy for antiparasitic drug discovery.

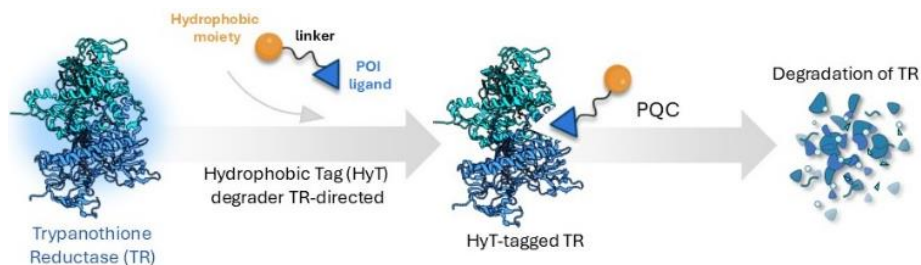


Figure 1. A schematic of protein degradations induced by Hydrophobic Tag Degradation. POI represents the protein of interest and PQC represents protein quality control machinery in cells to degrade the proteins.

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FC12

DNA POLYMERASE η INHIBITORS AGAINST CANCER CHEMORESISTANCE

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Drug resistance is a major challenge in cancer therapy and a leading cause of cancer-related mortality. Human DNA polymerase eta (Pol η) contributes to chemoresistance by enabling translesion DNA synthesis (TLS) across bulky cisplatin-induced DNA lesions, thereby reducing drug efficacy [1]. In this context, targeting Pol η represents a compelling strategy to restore chemosensitivity in TLS-dependent tumors, including ovarian cancer and melanoma.

Here, we report the discovery and characterization of a new class of 44 Pol η inhibitors with good potency and a promising drug-like profile, inspired by our prior drug discovery efforts [2]. Data from preliminary cell viability assays indicate that Pol η inhibition increases cisplatin sensitivity in Pol η -proficient cell lines, and the cellular response is consistent with SAR trends observed in biochemical gel elongation assays. Further cellular studies are underway to further validate the mechanism of action of the most promising compounds, including **ARN25087**. In addition, we conducted a virtual screening campaign targeting a newly identified Pol η allosteric pocket containing Trp297. This residue is unique to Pol η (not conserved in other polymerases) and therefore could be targeted by highly selective, allosteric Pol η inhibitors [3]. So far, we have successfully identified 3 chemically distinct hits. Based on their synthetic tractability, we initiated a drug discovery campaign starting from **ARN18532**, with an IC_{50} of $41.4 \pm 4.7 \mu M$. Medicinal chemistry efforts to validate our additional hits are currently ongoing. In conclusion, we established a robust drug discovery pipeline identifying compounds suitable for future lead optimization, and we are currently investigating a new series of putative allosteric inhibitors to expand the Pol η inhibitor landscape (Figure 1).

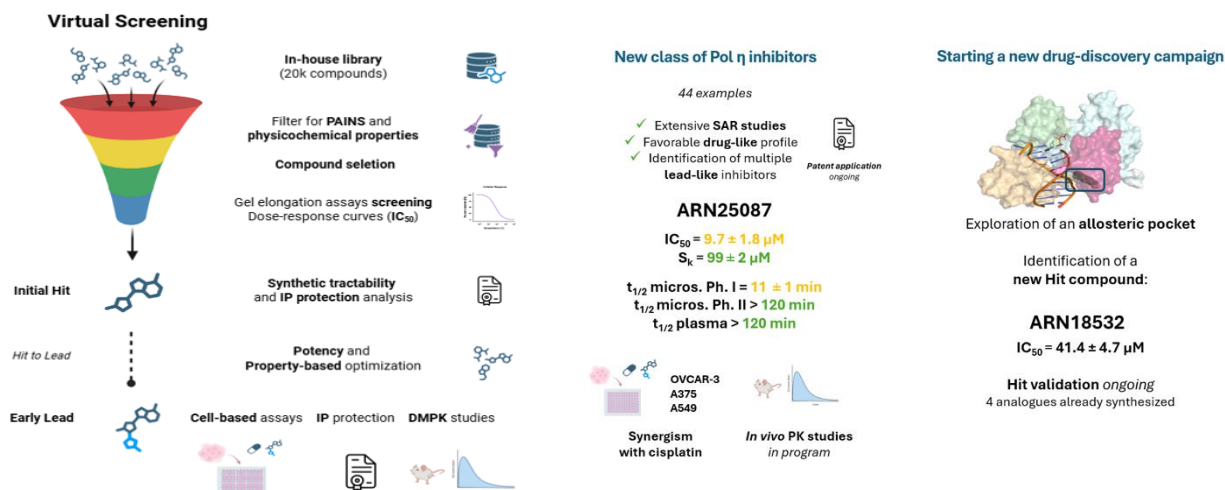


Figure 1: Overall project pipeline and key achievements of ongoing classes of Pol η inhibitors. Metabolic stability assays were performed using mouse microsomes and plasma proteins.

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FC13

GREENING PROTEOLYSIS TARGETING CHIMERA DEVELOPMENT: CASHEW NUTSHELL LIQUID-BASED CEREBLON LIGANDS

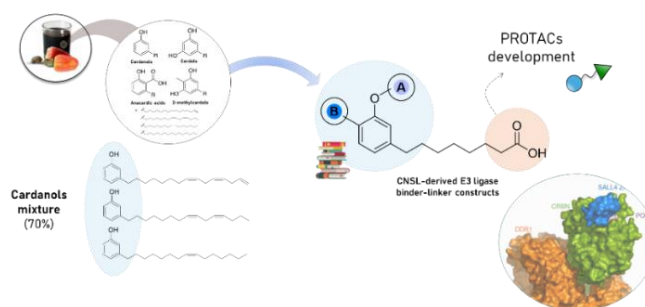
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The use of biowaste in medicinal chemistry is gaining increasing attention as a strategy to improve the sustainability of drug discovery. In this context, we present its application to PROteolysis TArgeting Chimeras (PROTACs), a promising class of heterobifunctional molecules that induce targeted protein degradation via the ubiquitin-proteasome system.¹ Despite their therapeutic potential,² PROTAC development usually involves labour-intensive multistep synthesis and purification, often associated with low yields, high solvent consumption, and significant chemical waste, making current workflows poorly aligned with green chemistry principles. To address these challenges, we propose a novel strategy based on cashew nutshell liquid (CNSL), an abundant agro-industrial by-product generated during the processing of *Anacardium occidentale*. CNSL is a renewable source of phenolic compounds, including cardanols, cardols, 2-methylcardols, and anacardic acids which are characterised by a pentadecyl alkyl side chain with variable unsaturation. Remarkably, CNSL has been successfully exploited for the development of antiparasitic compounds.^{3,4} Leveraging these structural features, we designed CNSL-based CRBN binder-linker constructs (CNSL-CRBN-BLCs) as sustainable and synthetically accessible alternatives to traditional CRBN recruiters (e.g., thalidomide) (Figure 1). Notably, the intrinsic aliphatic chain of these compounds can serve as a built-in linker, enabling a more streamlined and potentially greener assembly of PROTACs. Molecular docking studies confirmed the compatibility of the CNSL-derived scaffolds with the CRBN binding site, supporting their potential as E3 ligase ligands. To date, eight CNSL-CRBN-BLC derivatives have been successfully synthesised following a strategy guided by green chemistry principles. Preliminary differential scanning fluorimetry (DSF) studies on the CRBN^{mid} construct revealed target engagement for the most promising CNSL-derived compound.⁵ The lead candidate has been conjugated to the BRD4 inhibitor JQ1 in order to develop *proof-of-concept* BRD4-degrading PROTACs,⁶ whose degradation activity is being assessed by Western blot analysis. Overall, this approach establishes CNSL as a renewable platform for the development of next-generation CRBN ligands, while also highlighting viable route towards more sustainable PROTAC design.



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FC14

DISCOVERY OF NEW HETEROCYCLIC COMPOUNDS AS METALLO- β -LACTAMASE INHIBITORS TO REVERSE ANTIMICROBIAL RESISTANCE

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Antimicrobial resistance (AMR) is currently one of the major challenges in public health. Among the different mechanisms involved in AMR, the most widespread and concerning is the expression of metallo- β -lactamases (MBLs). MBLs present one or two zinc ions in the active site, which are responsible for inactivating β -lactam antibiotics, including carbapenems, the last-resort agents. In particular, New Delhi metallo- β -lactamase-1 (NDM-1), Verona integron-encoded MBLs (VIM), and Imipenemase (IMP) are the most clinically relevant B1 MBLs. A promising strategy to overcome MBL-mediated carbapenem resistance is the co-administration of β -lactam antibiotics with MBL inhibitors (MBLIs). Several MBLIs, carrying one or more zinc binding groups (ZBGs) to coordinate zinc ions, have been discovered [2], but none have reached clinical use. In our research group, we previously synthesized a series of compounds characterized by the 1,2,4-triazol-3-thione ring, a promising ZBG for MBLs [3], connected through a linker to different basic portions, that are fundamental for the interaction with the enzyme. To further investigate the chemical features essential for MBLs inhibition, selecting our most interesting NDM-1 inhibitor (Hit compound, Figure 1) which was inspired by the structure of different β -lactam antibiotics and known MBLIs [4], we designed new compounds by maintaining a propyl or phenyl linker (in green) connected to the 1,2,4-triazol-3-thione, and modifying the basic moiety (in blue) or replacing the phenyl ring (in red) with various aromatic and heteroaromatic systems. Moreover, in some compounds, the ZBG was replaced with bioisoster heterocycles, bearing a carboxylic group (Figure 1).

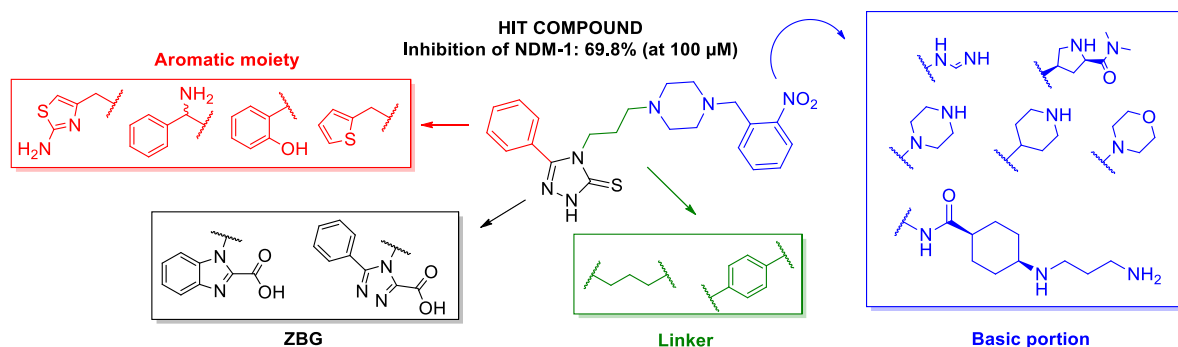


Figure 1: Structures of the designed MBL inhibitors.

The inhibitory activity of the synthesized compounds was evaluated through enzymatic assays on NDM-1, IMP-1 and VIM-2, and their synergistic effect with carbapenems was tested on MBL-producing laboratory strains and clinical isolates with characterized phenotypes. In addition, computational studies were performed to evaluate the interaction of the most promising derivatives with B1 MBLs.

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FC15

CHARACTERIZATION OF HYALURONIC ACID OLIGOMERS BY NMR SPECTROSCOPY

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Hyaluronic acid (HA) is a naturally occurring high molecular weight polymer in mammalian tissues, constituted of disaccharides (2-mer) repeating unit of *D*-glucuronic acid (GlcA) and *N*-acetyl-glucosamine (GlcNAc), linked by $\beta(1\rightarrow3)$ and $\beta(1\rightarrow4)$ glycosidic bond (Scheme 1). It is a key component of the extracellular matrix and provides a variety of different biological and structural functions. HA is largely metabolised by the gut microbiome to low molecular weight oligomers (LMWOs) [1], which are gaining interest in the scientific community for their role on regulating inflammatory and tumoral mechanisms, as well as their semisynthetic bioactive derivatives. Therefore, access to well characterized HA oligomers is essential, particularly saturated species that are not currently commercially available.

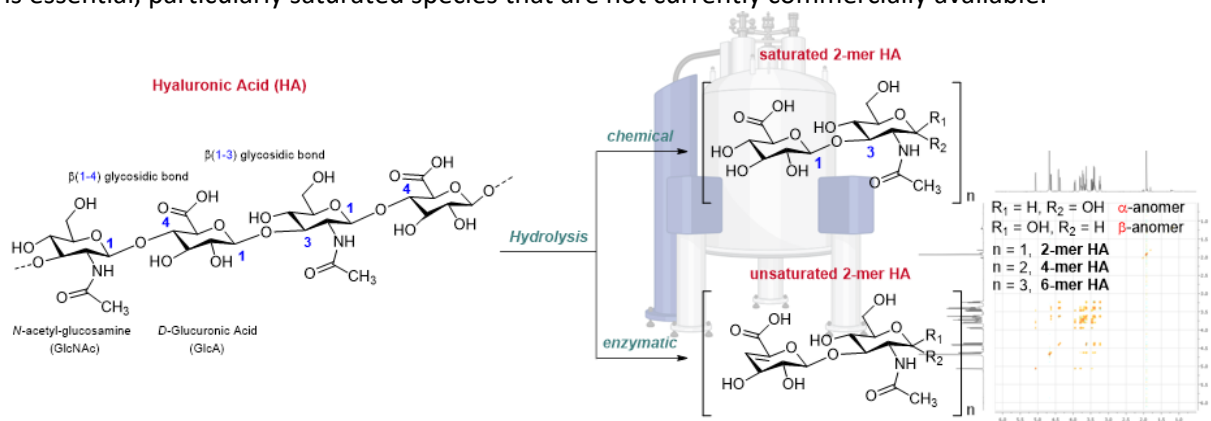


Figure 1. Hydrolysis of HA 200KDa using chemical and enzymatic reactions, resulting respectively in saturated and unsaturated oligomers.

Based on these considerations, a reproducible method for the preparation, purification and characterization of LMWOs, has been developed. Both chemical and enzymatic hydrolysis of HA were investigated. Saturated oligomers were isolated under chemical hydrolytic conditions, whereas unsaturated oligomers were obtained via enzymatic approach. An extensive NMR study, performed on a 600 MHz spectrometer, was dedicated to assessing the structural features of the isolated LMWOs. ¹H- and ¹³C-NMR one-dimensional analysis, ¹H-¹H homonuclear COSY, TOCSY, NOESY and ¹H-¹³C heteronuclear HSQC, HMBC two-dimensional investigations, were conducted in D₂O. Specifically, ¹H-NMR spectrum allowed to define the presence and ratio of α and β anomers, while COSY and HSQC spectra confirmed the $\beta(1\rightarrow4)$ glycosidic cleavage [2].

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FC16

NON-AGONIST MODULATION OF PPAR γ AS A STRATEGY FOR INSULIN RESISTANCE

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Insulin resistance is a condition characterised by a reduced cellular response to insulin, despite normal or increased hormone levels. It represents a central feature of type 2 diabetes mellitus and metabolic syndrome, two highly prevalent disorders with major clinical and socioeconomic impact. Classical PPAR γ agonists, such as glitazones, are effective insulin sensitisers, but their clinical use has been limited by adverse effects associated with full receptor activation. Therefore, non-agonist PPAR γ modulators able to improve insulin sensitivity without triggering the canonical agonist profile represent an attractive therapeutic opportunity [1].

A promising strategy relies on the inhibition of PPAR γ phosphorylation mediated by CDK5. This mechanism is associated with the stabilization of the β -sheet region of PPAR γ containing Ser245, thereby counteracting post-translational modifications linked to insulin resistance without triggering the transcriptional profile of PPAR γ agonists. In a previous work, we identified 4-(4-bromophenyl)-3-hydroxy-5-(3-hydroxyphenyl)furan-2(5H)-one as a non-agonist PPAR γ modulator capable of preventing receptor phosphorylation without directly inhibiting either CDK5 or PPAR γ [1].

Starting from this compound, we applied structure-based design approaches to develop new derivatives with improved affinity for PPAR γ . The resulting compounds displayed dissociation constants in the nanomolar range, improving PPAR γ affinity by more than one order of magnitude compared with the parent molecule [2]. In parallel, a bioisosteric optimization strategy was applied to enhance compound stability, with the aim of improving their pharmacokinetic potential while preserving the desired non-agonist mechanism of action.

The most promising derivative is currently being evaluated in adipocyte-based cellular models to assess its impact on intracellular lipid accumulation. These findings highlight the potential of structure-guided γ -hydroxy lactone derivatives as non-agonist PPAR γ modulators and provide the basis for ongoing studies aimed at defining their metabolic profile.

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FC17

NOVEL THIAZOLIDINONE-ISATIN HYBRIDS POTENTLY INHIBIT hCA IX AND ENHANCE DOXORUBICIN-INDUCED APOPTOSIS IN HYPOXIC GLIOBLASTOMA CELLS

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Carbonic anhydrase IX (hCA IX) is a HIF-1 α -regulated transmembrane zinc-metalloenzyme overexpressed in hypoxic solid tumors, where it promotes extracellular acidification, invasive migration, and chemoresistance [1]. Its overexpression in glioblastoma multiforme (GBM) correlates with poor prognosis [2,3], yet no hCA IX inhibitor has reached clinical approval, underscoring the need for potent, isoform-selective compounds.

We designed and synthesized a series of thiazolidinone-isatin hybrids bearing a benzenesulfonamide zinc-binding group (3a-i), along with the corresponding N-acetylated derivatives (4a-i). Enzymatic evaluation identified 3f as the most potent and selective hCA IX inhibitor (K_i = 8.6 nM; SI hCAI/IX = 631; SI hCAII/IX = 32.7). Sulfonamide N-acetylation completely abolished activity across all derivatives (K_i > 10,000 nM). Molecular docking studies of 3f evidenced zinc ion binding and key hydrogen-bond interactions. The biological potential of 3f was assessed in T98G glioblastoma cells under a $CoCl_2$ -based chemical hypoxia model, confirmed by Western blot analysis (Figure 1A). T98G cells exhibited intrinsic resistance to doxorubicin (Doxo 5 μ M, cell viability ~76%). Co-treatment with sub-cytotoxic concentrations (5 μ M) of 3f markedly sensitized T98G cells to doxorubicin, reducing cell viability to ~43% under normoxia and ~39% under hypoxia (Figure 1B). Western blot analysis revealed activation of the intrinsic apoptotic pathway, with increased Bax/Bcl-2 and cleaved caspase-3 ratios and maximal pro-apoptotic signaling under the triple combination of $CoCl_2$, 3f, and doxorubicin. These findings identify 3f as a promising lead compound for CA IX-targeted therapy in hypoxic, chemoresistant glioblastoma.

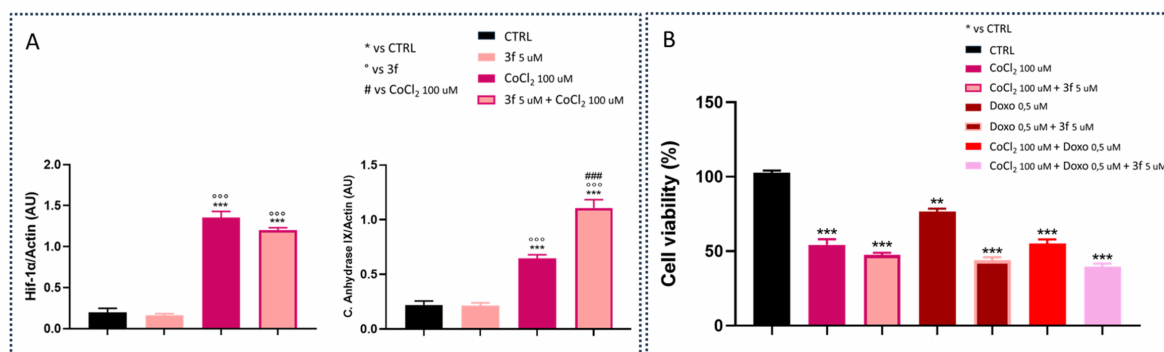


Figure 1. Hypoxia model validation and antiproliferative activity of 3f in T98G cells. (A) Western blot of HIF-1 α and CA IX under normoxia and hypoxia $\pm$ 3f. (B) Cell viability (MTT, 24 h) following doxo $\pm$ 3f under normoxic and hypoxic conditions. Data are expressed as mean $\pm$ SEM. **p < 0.01, ***p < 0.001 vs CTRL.

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7 N 15 P 6 C 9 F 17

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FC18

**MULTITARGET HYBRID SMALL MOLECULES FOR METAL CHELATION WITH ADDITIVE
CHOLINESTERASE INHIBITORY AND ANTIOXIDANT PROPERTIES IN ALZHEIMER'S DISEASE**

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Alzheimer's disease (AD) is strongly associated with the misfolding and aggregation of amyloid- β (A β) peptides, a process significantly influenced by metal dyshomeostasis.[1] In particular, copper ions play a crucial role by modulating aggregation pathways and promoting oxidative stress through redox cycling. [1] Recent studies have shown that small molecules capable of interacting with metal ions can effectively influence A β aggregation, not through simple chelation but by modulating metal-protein interactions under biologically relevant conditions. [1] These compounds are able to alter aggregation kinetics, reduce the formation of toxic oligomeric species, and mitigate metal-induced oxidative damage. [1] This approach highlights the potential of metal-targeting small molecules as a strategy to control A β -related toxicity and provides a mechanistic framework for the development of new disease-modifying agents in AD [1-3]. Starting from lead compounds reported in recently published studies, we have designed and synthesized hybrid molecules with a multitarget profile incorporating chelating moieties. [2,3] The inclusion, within their structures, of pharmacophoric elements derived from well-known drugs such as donepezil, rivastigmine, and tacrine allowed us to retain activity toward classical targets, particularly cholinesterases, while simultaneously addressing metal-mediated pathological pathways [2,3]. The obtained results are very encouraging, highlighting a well-defined selectivity trend toward Fe (III), Cu (II), and Zn (II). Moreover, the compounds retain inhibitory activity against one or both cholinesterases and, in some cases, exhibit significant antioxidant properties, further supporting their potential as multifunctional agents in AD therapy.

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FC19

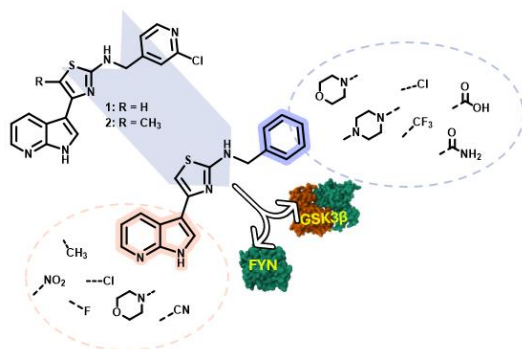
TARGETING FYN AND GSK-3 β TO TACKLE NEURODEGENERATION

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The complex etiopathology of neurodegenerative diseases still lacks effective treatments able to halt the cognitive/motor decline, therefore the chance to intervene with potential treatment able to merge neuromodulatory and neuroprotective properties could result in amplified therapeutic effect, favoring the shift from neurodegeneration to neuroregeneration. To this aim, Fyn proto-oncogene kinase (Fyn) and Glycogen synthase kinase 3 β (GSK-3 β) emerged as promising targets for their multiple involvement in modulating brain physiopathological conditions, in addition to be physiologically involved in synaptic plasticity and glial cell formation.^{1,2} In this context, we previously developed submicromolar Fyn/GSK-3 β



dual inhibitors which demonstrated promising neuromodulatory and neuroprotective properties, ascribing different activity to the modulation of each kinase and confirming the potential of this approach (Figure 1).³

Herein, we report a second round of rationally-designed SAR exploration looking for more potent and selective Fyn/GSK-3 β dual inhibitors, before further proceed into extensive evaluation in different neuronal/glial diseased models. In this regard, we mainly focused on the benzyl tail and azaindole nucleus, by introducing different hydrophilic moieties, halogens or electron-withdrawing groups, with the aim

to fully explore the available chemical space within the two binding sites. Regarding benzyl substituents, various basic hydrophilic groups were introduced by means of different junctions to potentially engage solvent-facing surface of the two kinases, while small substituents into the azaindole core were mainly evaluated in position 5 as it previously emerged as key driver for selectivity.

Interestingly, the inserted substituents highlighted new promising insights for future optimizations. Particularly, new clues to achieve more potent Fyn selective and dual inhibitors were identified, while biological investigations are ongoing to evaluate the neuroprotective potential of new derivatives as well as the development of a new series merging the old and new optimized structural requirements.

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XXX

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FC20

DUAL SARS-CoV-2 NSP13 HELICASE FUNCTIONS INHIBITORS EXHIBITING ADDITIVE ANTIVIRAL ACTIVITY AS A PROOF OF CONCEPT FOR COMBINATION THERAPY

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Helicase of human coronaviruses (hCoVs) is responsible for the RNA unwinding in a 5' to 3' direction, a process driven by the ATP hydrolysis. Given its crucial role in viral replication and its highly conserved sequence among hCoVs, this enzyme represents a promising and attractive target for the development of new antiviral drugs. [1]

In this study, with the goal to identify potential Pan-hCoVs helicase inhibitors, we have rationally designed and synthesized a library of compounds. These compounds were characterized using structural (single-crystal X-ray diffraction) and spectroscopic (NMR, MS) techniques and subsequently, evaluated for their biological activity. Several compounds displayed low-micromolar IC₅₀ values against both nsp13 NTPase and unwinding activities. Among these, **3i** emerged as the lead compound, combining enzymatic inhibition (IC₅₀ unwinding $2.15 \pm 0.19 \mu\text{M}$ and IC₅₀ NTPase $8.52 \pm 0.68 \mu\text{M}$) with a favourable antiviral activity/cytotoxicity profile in two complementary cell models of SARS-CoV-2 infection (EC₅₀ $23.80 \pm 1.80 \mu\text{M}$ in VeroE6-GFP, SI 18.15 folds; EC₅₀ and $6.7 \mu\text{M}$ in Calu3 cells, a human lung epithelial model). The compound further demonstrated absence of hepatocellular toxicity in HepG2 cells, negligible inhibition of human helicases DDX3X and DDX5, and acceptable drug-like properties from biomimetic HPLC, and *in silico* ADMET evaluation. The metabolic stability of the compound was also evaluated through microsomal stability assays in both human and rat liver microsomes. Binding affinity evaluation by SPR confirmed a K_D value of $6.20 \mu\text{M}$, while enzyme kinetic studies indicated mixed-type NTPase inhibition, further corroborated by biochemical assays and molecular dynamics simulations.

Finally, **3i** showed additive antiviral effects with Remdesivir or Nirmatrelvir, mirroring established combination strategies in antiviral therapy, and supporting its potential for the development of broad-spectrum coronavirus therapeutics. These findings underscore the potential of targeting hCoVs helicase as a strategy for developing effective treatments against SARS-CoV-2 and other hCoVs, opening the door to the development of novel therapeutic agents that could address both current and future emerging coronavirus-related diseases.

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Messina, Italy - September 13-16, 2026

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FC21

DEFLAZACORT-H₂S DONOR HYBRIDS: A DUAL ANTI-INFLAMMATORY AND ANTIOXIDANT APPROACH FOR DUCHENNE MUSCULAR DYSTROPHY

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Duchenne muscular dystrophy (DMD) is a lethal X-linked disease characterized by chronic inflammation, oxidative stress, skeletal muscle weakness and functional decline. Glucocorticoids represent the drugs of choice for DMD treatment, although long-term therapy is limited by significant adverse effects.

Hydrogen sulfide (H₂S) has well-known anti-inflammatory and antioxidant properties, and impaired H₂S signaling has been documented in dystrophic muscle. Restoration of H₂S levels can improve skeletal muscle function in several preclinical models [1].

In this study, through a molecular hybridization approach, deflazacort was chemically conjugated to H₂S-donors aimed at preserving its anti-inflammatory activity and incorporating controlled sulfide-mediated redox modulation. Five deflazacort-H₂S donor hybrids (**I–V**) were designed, synthesized and fully pharmacologically characterized. All compounds were analyzed for their chemical and enzymatic stability in different media, as well as for their sulfide-releasing properties by an amperometric approach. The hybrids displayed high chemical stability under physiological and acidic environments, whereas enzymatic stability in serum-containing medium revealed differences according to the linker and donor structure. The derivative **IV** exhibited the longest half-life and a slow, L-cysteine-dependent H₂S release profile, consistent with controlled sulfide delivery.

The anti-inflammatory and anti-oxidant activity of the hybrids was evaluated in C2C12 myotubes exposed to LPS+IFN- γ . Compound **IV**, not only significantly reduced NOx production, but also induced a complete downregulation of key pro-inflammatory and pro-oxidant genes. Unlike the active metabolite of the corticosteroid, the Deflazacort-H₂S donor hybrid was able to markedly reduce intracellular ROS levels.

In *mdx* mice, compound **IV** (0.6 mg/Kg), administered at half dosage of deflazacort (1.2 mg/Kg), restored locomotor performance to the same extent as deflazacort. In addition, the reduction of H₂O₂ levels and the increase of glutathione redox ratio (GSH/GSSG) *in vivo* confirmed the dual activity of compound **IV**.

These results demonstrate the effectiveness of molecular hybridization in drug design strategy and identify compound **IV** as a dual-acting hybrid that combines anti-inflammatory activity with sustained antioxidant modulation, thus representing a promising dose-sparing approach for DMD treatment.

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DEVELOPMENT OF NOVEL PEPTIDE-BASED MICHAEL ACCEPTORS TARGETING RHODESAIN OF *TRYPANOSOMA BRUCEI* RHODESIENSE

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Human African Trypanosomiasis (HAT) is a Neglected Tropical Disease (NTD) endemic in sub-Saharan Africa, it remains a significant cause of mortality despite a marked decline in reported cases in recent years, mainly caused by *Trypanosoma brucei gambiense* and *rhodesiense*, responsible for a chronic and acute form of the disease, respectively [1]. Despite recent advances, the risk of drug resistance and the need for safer therapies highlight the importance of new targets for drug discovery. In this context, rhodesain, a cathepsin L-like cysteine protease, is a promising target for the development of novel antitrypanosomal agents, since it is essential for parasite survival, blood–brain barrier crossing, immune evasion, and protein turnover.

Over the past years, our research group has been actively involved in the development of novel rhodesain inhibitors [2,3], leading to the identification of a highly potent dipeptide inhibitor, e.g. lead compound **1** (Figure 1), endowed with an impressive K_i =16 nM [4]. Starting from this lead structure, a new series of dipeptide inhibitors was designed to explore the potential role of α,β -unsaturated warhead, which has been reported to covalently trap the active site thiol function, leading to an inactivation of rhodesain. In the present study, homophenylalanine (hPhe) was retained at the P1 position due to its critical contribution to enzyme affinity, while cyclohexylalanine (Cha) or leucine residues were explored at the P2 site in agreement with rhodesain substrate preferences. The P2 amino group was capped with a fluorobenzoyl moiety spanning into the P3 region to optimize interactions within the S3 pocket. Herein, we present the synthesis of dipeptide nitriles **2–3a–g**, together with their biological evaluation against rhodesain and molecular modeling investigations undertaken to elucidate the structure–activity relationship (SAR).

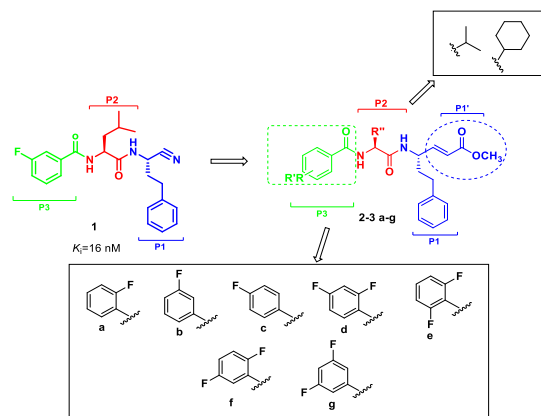


Figure 1. Structure of lead compound **1** and of dipeptide nitriles **2-3 a-g**.

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XXX

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XXX

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P001

DESIGN AND SYNTHESIS OF A LIBRARY OF THALIDOMIDE-BASED PROTEOLYSIS TARGETING CHIMERAS (PROTACS) AS ANTIVIRAL AGENTS

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Flaviviruses are vector-borne RNA viruses primarily transmitted by mosquitoes that cause severe diseases, such as West Nile, Dengue and Zika.¹ These diseases represent a major global public health concern, affecting millions of people each year. Their spread is strongly influenced by three main megatrends: urbanization, climate change, and increasing intercontinental travel.

The absence of drugs available for the treatment of these infections and the limitation of existing therapeutic strategies to prevention highlight the urgent need for the development of novel antiviral agents.² In this research project, we adopted an innovative therapeutic strategy based on the selective degradation of target proteins, known as Proteolysis Targeting Chimeras (PROTACS).³ PROTACS are heterobifunctional molecules composed of a ligand for the protein of interest (POI) and a binder for an E3 ubiquitin ligase, connected through a suitable linker. PROTACS hold significant promise for antiviral drug development.⁴ In this work, the selected E3 ligase was cereblon (CRBN), while the POI was the NS2B–NS3 serine protease, an essential component of the viral replication cycle.⁵ The high degree of conservation of NS2B–NS3 among West Nile, Dengue, and Zika viruses enables the development of broad-spectrum PROTACS potentially effective against multiple flaviviruses.⁵

Therefore, the aim of this thesis was the design and synthesis of CRBN-recruiting PROTACS by varying the length and chemical nature of the linker: we used alkyl and PEG chains to obtain flexible linkers, as well as heteroaromatic rings to obtain shorter and more rigid ones. Specifically, different new synthetic strategies were explored and optimized, leading to the synthesis of seven final compounds featuring thalidomide as the typical E3 ligase-recruiting moiety: MAC40, MAC63, MAC64, MAC29, MAC62, MAC65 and MAC38.

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XXX

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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P002

DEVELOPMENT OF INNOVATIVE COMPOUNDS TARGETING SARS-CoV-2 NSP13

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The coronavirus disease 19 (COVID-19), caused by SARS-CoV-2, has represented a major challenge for the global scientific community in recent years.^[1] Despite the availability of vaccines and therapeutic agents for COVID-19, it remains a significant global health threat, and no highly effective and specific antiviral therapy is currently available. Among the viral proteins, the non-structural protein 13 (nsp13) represents an attractive drug target because of its essential role in viral replication and its high conservation across coronaviruses.^[2] Nsp13 is involved in the unwinding of viral nucleic acids through nucleotide triphosphates hydrolysis. Inhibition of these functions compromises the virus's ability to replicate. Therefore, targeting nsp13 offers an attractive opportunity for the development of broad-spectrum antiviral agents.^[3] Given the urgent need for new antivirals, targeted protein degraders represent a promising strategy, as they enable the selective elimination of conserved viral proteins essential for the viral replication.^[4] This emerging therapeutic approach relies on small molecules able to recruit the cellular ubiquitin–proteasome system, leading to the degradation of specific target proteins. Notably, a series of aryl diketo acid (DKA) derivatives have been reported as inhibitors of SARS-CoV-2 nsp13. In our previous studies, considering the limitations associated with DKAs, we identified a series of non-DKA small molecules able to inhibit nsp13-associated enzymatic activities, providing promising micromolar hit compounds. Subsequently, structure–activity relationships (SAR) studies were conducted through the synthesis and biological evaluation of various analogues, aiming to optimize inhibition of both enzymatic activities. Furthermore, the hit compound and the most active derivatives were also investigated in infected cells. Building on these encouraging results, selected nsp13 inhibitors were further exploited for the design of targeted protein degraders. Accordingly, a novel series of compounds was designed and synthesized, in order to explore the structure–activity relationships of these bifunctional molecules. The new compounds were tested by our collaborators.

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P003

DESIGNING A NEW-GENERATION OF GLS1 ALLOSTERIC INHIBITORS BASED ON IN SILICO FRAGMENT-BASED STRATEGY

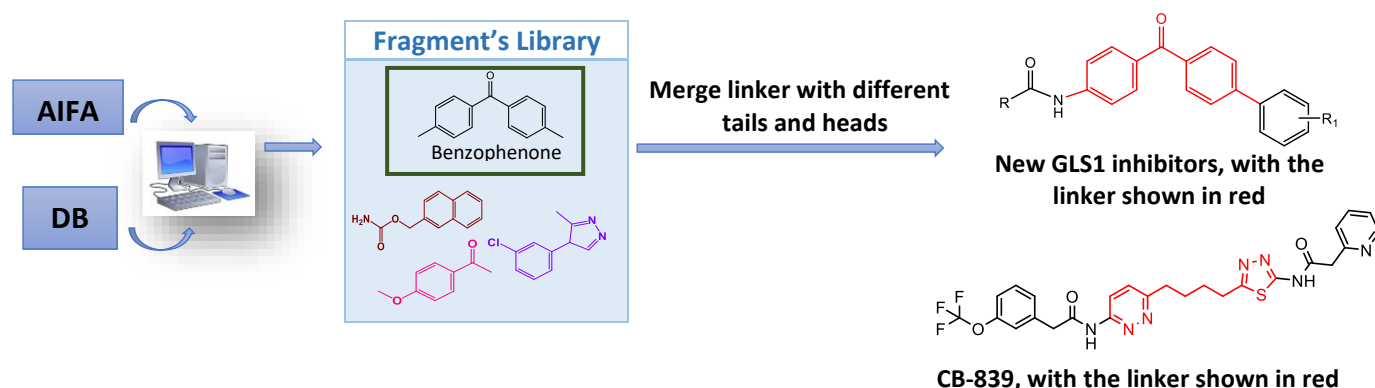
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Many tumors depend on glutamine to support their growth and proliferation, biosynthesis, redox balance, and energy production. Glutaminase (GLS1), a mitochondrial enzyme that catalyzes the hydrolysis of glutamine to glutamate, is upregulated in many cancers, making it a promising therapeutic target. Several GLS1 inhibitors have been developed so far, and are classified according to their mechanism of action, mainly as substrate active site inhibitors and allosteric site inhibitors (the so-called BPTES). Among the latest, CB-839 and IPN60090 are in clinical trials for the treatment of solid tumors [1]. To date, the chemical space explored for GLS1 allosteric inhibitors is quite restricted, largely based on scaffolds derived from CB-839 and BPTES. Unfortunately, many of these compounds pose significant challenges in terms of solubility and bioavailability. Therefore, researching more structurally diverse new candidates remains an important and only partially addressed need in this field. On this basis, we have already developed a class of ligands using generative AI on a BPTES dataset [2]. A second set of inhibitors is currently in development, applying a fragment-based drug design approach that uses AIFA and Drug Bank drugs, guided by previous results and chemical synthesis data. All related GLS1 allosteric inhibitors consist of a head, a linker, and a tail, adopting a U-shaped conformation, which enables enzyme inactivation. Among the new ligands, a new linker scaffold emerged. Derivatives with a benzophenone linker (**Fig. 1**) show binding energies and structural overlap closely analogous to those observed for CB-839.



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XXX

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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P004

INHIBITION OF FTSJ1 BY 1,2,4-TRIAZOLE DERIVATIVES AS A MECHANISM FOR TRANSLATIONAL READTHROUGH: AN INTEGRATED COMPUTATIONAL AND EXPERIMENTAL STUDY

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Nonsense mutations introduce premature stop codons that result in truncated, nonfunctional proteins and are frequently associated with tumor suppressor genes such as TP53 [1]. Translational readthrough-inducing drugs (TRIDs) represent a promising therapeutic strategy to restore the expression of full-length functional proteins. Among the factors regulating translational fidelity, FTSJ1, a tRNA 2'-O-methyltransferase, has recently emerged as a potential target for promoting translational readthrough through inhibition of its activity [2]. In this study, four 1,2,4-triazole-based TRIDs (IP14, IP15, IP17, and IP18) were investigated using an integrated computational and experimental workflow. A homology model of FTSJ1 was generated and refined prior to computational studies. Ligand binding was evaluated through induced-fit docking, binding pose meta dynamics, and molecular dynamics simulations to investigate binding stability and protein-ligand interactions [3, 4]. Among the tested compounds, IP17 and IP18 exhibited improved binding stability and more favorable MM-GBSA binding free energies compared with the reference inhibitor DAP, suggesting stronger engagement with FTSJ1 [5]. In HeLa pFLuc190UGA cells, all compounds increased luminescence levels consistent with enhanced translational readthrough, while FTSJ1 overexpression significantly reduced this effect. Collectively, these findings support FTSJ1 as a promising target for modulating translational readthrough and identify 1,2,4-triazole derivatives, particularly IP17 and IP18, as potential scaffolds for nonsense mutation suppression.

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P005

DEVELOPMENT OF PFKFB3 KINASE COVALENT INHIBITORS WITH ANTITUMOR ACTIVITY

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Pancreatic ductal adenocarcinoma (PDAC) is an extremely aggressive form of cancer associated with a very poor prognosis. Its progression is strongly supported by metabolic reprogramming, which has made cancer metabolism an appealing target for therapeutic intervention. However, treatments aimed at blocking glycolysis have shown important clinical drawbacks, mainly because of their toxicity. Targeting 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB), especially the PFKFB3 isoform, could represent a safer alternative. [1] Inhibition of PFKFB3 reduces glycolytic activity to basal levels rather than completely suppressing it, providing a potentially broad therapeutic window and representing a promising strategy for PDAC treatment.[2]

We report the first covalent inhibitor of PFKFB3, incorporating moderately reactive, drug-like warhead that target the previously unexplored Cys154 residue within the enzyme active site (Figure 1). Biochemical assays confirmed both irreversible inhibition and covalent binding. The lead compound selectively reduced viability across multiple PDAC cell lines and, in vivo, significantly suppressed tumor growth in zebrafish xenograft models, underscoring its potent and specific antitumor activity. Furthermore, this covalent ligand exhibited a pronounced synergistic effect when combined with the chemotherapeutic agents fluorouracil or gemcitabine, which are standard-of-care treatments for PDAC. Overall, this work introduces a novel covalent PFKFB3 inhibitor and further supports anti-glycolytic therapy as a promising strategy for PDAC treatment. [3]

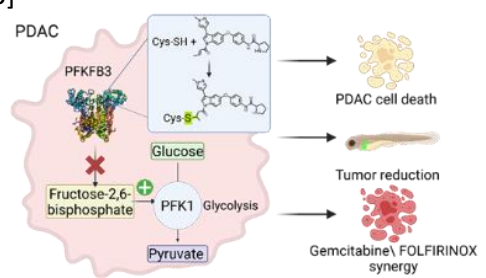


Figure 1. Development of covalent inhibitor targeting PFKFB3

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P006

EFFICIENT SYNTHESIS OF THE KINASE INHIBITOR NVS-PI3-4 USING FLOW CHEMISTRY, MICROWAVE IRRADIATION, AND IMMOBILIZED REAGENTS

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Phosphatidylinositol 3-kinases (PI3Ks) are a family of intracellular lipid kinases involved in the regulation of several essential cellular processes, including cell growth, proliferation, survival, metabolism and motility, through the generation of secondary messengers that activate downstream intracellular signalling pathways [1]. Their dysregulation is strictly related to the arising of various cancers, making them attractive targets for anticancer drug discovery. PI3Ks are classified into three classes (I, II, III) with class I further divided into IA heterodimers. The selective inhibition of PI3K γ , which has a pivotal role in leukocytes recruitment, has emerged as a promising strategy to modulate cancer progression while minimizing off-target effects and improving the safety and tolerability of therapeutic agents [2].

Nowadays, only few selective PI3K γ inhibitors are currently available (AS-604850, NVS-PI3-4, IPI-549, and AZ2). NVS-PI3-4 (chemical structure in Figure 1) was originally developed by Novartis and, besides being an invaluable pharmacological tool, it also represents a good model for the design of optimized derivatives (Figure 1) [3]. Unfortunately, its reported synthetic route includes several steps that negatively affect the overall efficiency of the process, such as a time-consuming amine protection step, the use of a homogeneous palladium catalyst, and the employment of *N,N'*-carbonyldiimidazole for urea formation. Therefore, the development of improved synthetic strategies toward NVS-PI3-4 and its analogues represents an important objective of our research. Guided by the principles of Green Chemistry, which aim to reduce the use of hazardous substances and promote more sustainable chemical processes, we developed an improved synthetic strategy for NVS-PI3-4 by exploiting different enabling technologies (Figure 1). In particular, the use of an immobilized catalyst, microwave-assisted synthesis, and flow chemistry allowed us to overcome key limitations of the original route, providing a more efficient, sustainable, and scalable approach to the preparation of this promising PI3K γ inhibitor and future novel analogues.

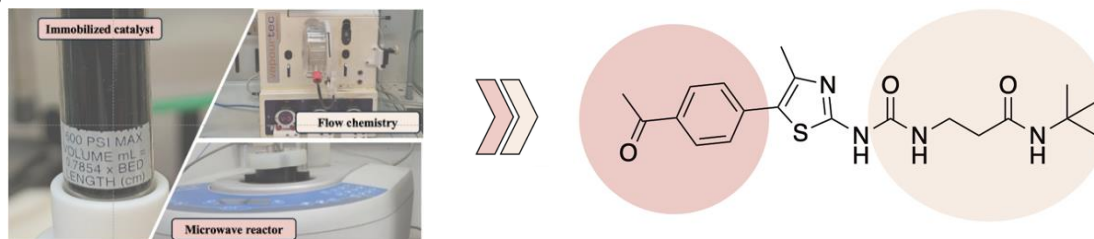


Figure 1. Enabling technologies for the synthesis of NVS-PI3-4 and novel derivatives.

Acknowledgment: This work was supported by Fondo Italiano per la Scienza FIS2 (grant number, FIS-2023-02269) from Italian Ministry of University and Research (to C.B.) and by Regione Lombardia PR FESR 2021-2027 – “Collabora&Innova” – Project 6154644 – GREEN-TECH – “Applicazione di tecnologie innovative a basso impatto ambientale per lo sviluppo e l’ottimizzazione di processi chimici sostenibili” (to L.T.).

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P007

FROM MOLECULAR DESIGN TO NEUROPROTECTION: A JOURNEY THROUGH BENZO[b]THIOPHENE-BASED MAO-B INHIBITORS

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Neurodegenerative disorders represent an increasing burden in ageing societies. In Parkinson's disease, the elevated activity of hMAO-B contributes to oxidative stress and dopaminergic neurodegeneration, supporting selective hMAO-B inhibition as a valuable therapeutic strategy. Building on previous studies on benzofuran and benzothiophene-3-ol scaffolds¹, this work explores 2-arylbenzothiophene derivatives as novel candidates for neurodegeneration-oriented drug discovery (Figure 1). Screening against hMAO-A and hMAO-B identified compounds 4, 11, and 12 as the most promising inhibitors. These derivatives were further evaluated in preliminary cellular assays: while compound 4 showed significant cytotoxicity, associated with increased ROS production and potential mitochondrial liability, compounds 11 and 12 were well tolerated up to 100 μ M, displaying a safety profile comparable to (R)-(-)-Deprenyl. Notably, compound 12 exhibited antioxidant-like properties, significantly reducing basal ROS levels and showing modest neuroprotective effects after 24 h in SH-SY5Y cells exposed to 6-OHDA. Molecular modelling studies further supported the proposed binding modes. Overall, a novel class of 2-arylbenzothiophenes has been identified as selective, nanomolar hMAO-B inhibitors, with activity finely modulated by aryl substitution².

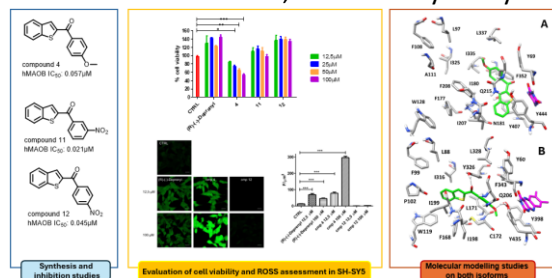


Figure 1. Work-flow of the project.

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<https://doi.org/10.3390/antiox15030346>



P008

REPURPOSING MEDICINAL CHEMISTRY CONCEPTS FOR TARGET-BASED DISCOVERY OF ANTI-XYLELLA FASTIDIOSA AGROCHEMICALS

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The limited availability of effective treatments against bacterial plant pathogens makes the discovery of sustainable agrochemicals a major challenge. In this context, medicinal chemistry concepts originally developed for human drug discovery, including target prioritization, ligand-based compound selection, target-engagement validation, and hit-to-lead perspectives, can be repurposed to support the rational identification of crop-protection agents.

Recently, we investigated a target-based discovery strategy aimed at identifying new agrochemical candidates against *Xylella fastidiosa* (*Xf*), a xylem-limited bacterial pathogen responsible for severe crop losses across Southern Europe, with a particularly dramatic impact on olive groves in Italy and lacking effective curative treatments.¹ Within this framework, filamenting temperature-sensitive Z protein (FtsZ), a well-validated bacterial cell division target, emerged as an attractive target for *Xf* with high conservation across the major *Xf* subspecies. Importantly, sequence alignment of *Xf* FtsZ with structurally characterized FtsZ homologues revealed differences in regions corresponding to known ligand-binding sites, suggesting the presence of exploitable sequence/structural features for the design of selective *Xf*-oriented inhibitors. Building on literature-reported FtsZ inhibitors from other organisms (e.g., *S. aureus* and *E. coli*), we selected representative reference compounds and complemented them with a similarity-based selection from a proprietary UniPg small-molecule library using 2D molecular similarity approaches. This medicinal chemistry-inspired selection strategy generated a focused compound set, which was submitted to *in vitro* validation as candidate inhibitors of *Xf* FtsZ, and, more broadly, as potential agrochemical hits.

Among the screened molecules, five inhibited planktonic growth, biofilm formation, and colony-forming unit formation. Dose–response assays on the best-performing compound showed activity against the three major *Xf* subspecies. Preliminary *in planta* assays in olive plants showed no phytotoxic effects after two months. Mechanistic studies by transmission electron microscopy revealed impaired cell division and increased cell size, consistent with perturbation of FtsZ-mediated cytokinesis, while surface plasmon resonance (SPR) experiments confirmed direct binding of the compound to recombinant FtsZ.

Overall, this study establishes a target-based discovery workflow for *X. fastidiosa*, integrating target prioritization, recombinant protein production, chemoinformatics-guided compound selection, biophysical target-engagement validation, and biological profiling. By translating medicinal chemistry logic into the agrochemical field, we identified an FtsZ-targeting hit active against *X. fastidiosa*, providing a rational starting point for deeper biological profiling, mechanistic validation, structure-guided optimization, and sustainable crop-protection development against this challenging plant pathogen.

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P009

FIRST-IN-CLASS SPIROOXINDOLE–SULFONAMIDE HYBRIDS AS TRIPLE-TARGET EGFR/CDK2/CA IX/XII INHIBITORS: POTENT ANTI-BREAST CANCER AGENTS WITH MULTIMODAL ACTION

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Aberrant activation of EGFR drives uncontrolled proliferation and survival in breast cancer, while CDK2 overrides cell cycle checkpoints, and tumor-associated carbonic anhydrases IX/XII sustain hypoxic adaptation and an acidic microenvironment. Co-targeting these three key regulators receptor signaling, cell cycle progression, and pH homeostasis offers a synergistic strategy to simultaneously block tumor growth, induce apoptosis, and circumvent resistance. Therefore, a single inhibitor capable of multitargeting EGFR, CDK2, and CA IX/XII presents a compelling therapeutic advantage over conventional single-target agents. The molecular design strategically combines distinct privileged structural motifs a challenge not previously addressed in the development of multitargeted anti-breast cancer agents. In this study, a novel class of triple-target EGFR/CDK2/CA IX/XII inhibitors were designed and synthesized by integrating a spirooxindole core with sulfonamide functionalities. An efficient one-pot, three-component [3+2] cycloaddition reaction enabled the construction of a focused library of thirty-two novel spirooxindole-pyrrolidine/pyrrolizidine compounds in excellent yields of up to 98%. Biological evaluation against carbonic anhydrase isoforms revealed a clear structure–activity relationship: derivatives featuring the sulfonamide zinc-binding group (–SO₂NH₂) demonstrated potent, nanomolar inhibition of tumor-associated isoforms hCA IX and XII. The most active carbonic anhydrase inhibitors (against CA I, II, IX, and XII) were subsequently subjected to EGFR and CDK2 inhibition assays, where they exhibited micromolar-range potency and greater efficacy compared to standard reference drugs. The most promising lead compounds, based on the spirooxindole–sulfonamide scaffold, inhibited the proliferation of triple-negative breast cancer (TNBC) cells, including the MDA-MB-231 model. This coordinated strategy aims to overwhelm cancer's adaptability, offering a promising rationale for overcoming the notorious resilience of TNBC [1-3].

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P010

MELATONIN-RELATED COMPOUNDS WITH ANTIOXIDANT AND NEUROPROTECTIVE PROPERTIES

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Melatonin (MLT), a hormone primarily known for its role in regulating circadian rhythms, has emerged as a powerful antioxidant with promising cytoprotective properties. Studies in cellular models demonstrate that MLT protects cells from toxic damage by direct scavenging free radicals, upregulating endogenous antioxidant defenses, and preserving mitochondrial function [1]. Accordingly, the neuroprotective potential of MLT has attracted increasing attention, particularly in Alzheimer's disease and Parkinson's disease neurodegenerative disorders where oxidative stress and mitochondrial dysfunction play a pivotal role in onset and progression [2]. Moreover, evidence suggests that exposure to environmental toxicants, including heavy metals such as cadmium (Cd), contributes to neurodegeneration through oxidative stress-mediated pathways [3]. These pleiotropic properties make MLT an attractive starting point for the design of novel multifunctional agents. In this context, a series of melatonin-related derivatives was designed and synthesized to explore their neuroprotective potential (Figure 1). Their biological evaluation included the assessment of antioxidant activity by measuring the ability to reduce intracellular ROS production, together with the investigation of their cytoprotective potential in complementary models of oxidative stress and neurotoxicity, including Cd-induced neuronal injury and Parkinson's disease-related cellular models induced by MPP⁺ and rotenone. Moreover, the ability of MLT and selected compounds to preserve mitochondrial function in Cd-exposed SH-SY5Y cells has been investigated. The results obtained with MLT and related synthesized compounds will be reported.

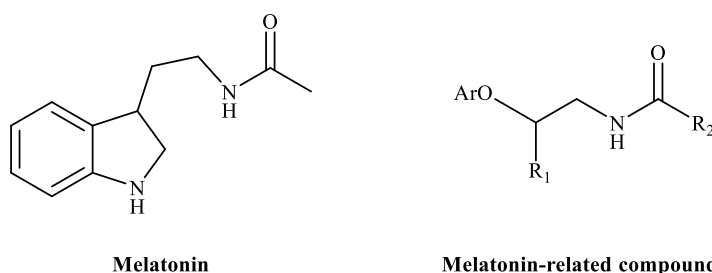


Figure 1. Melatonin and general structure of melatonin-related compounds

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P011

EXPLORING DISULFIDE BRIDGE AS A TOOL TO IMPROVE PIOGLITAZONE'S NEUROPROTECTIVE POTENTIAL: TOWARD THE DEVELOPMENT OF PROLONGED-ACTING MAO-B/PPAR γ MODULATORS

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Neurodegenerative diseases' treatments still represent one of the major unmet medical needs and their related clinical trials are characterized with one of the highest failure rates. Despite the promising preclinical premises, pioglitazone lies among those drugs that failed the clinical translation. It is an antidiabetic drug acting as PPAR γ agonist and later resettled as competitive and selective MAO-B inhibitor featuring polyhedral neuroprotective properties. In pursuing our efforts to broaden the therapeutic potential of pioglitazone toward the neurodegenerative context, we developed and preliminary characterized a new series of glitazone derivatives. Particularly, by means of different connectors, a disulfide warhead was attached to the 5-benzylthiazolidine-2,4-dione head to potentially engage cysteines located in MAO-B and PPAR γ binding sites and turn pioglitazone into a prolonged-acting modulator (Figure 1). Both MAO-B and PPAR γ hold cysteines proximal to pioglitazone's binding pose (*i.e.*, Cys172 and Cys285, respectively) within the two active sites,[1,2] that can be covalently trapped by the disulfide warhead through thiol-disulfide exchange reaction; thus, turning selective competitive modulators into targeted covalent ones could enhance their therapeutic potential thanks to the prolonged modulation of the same targets.[3] Interestingly, compound **5** emerged as a selective competitive MAO-B inhibitor and a PPAR γ agonist with a very slow dissociation rate, revealing a long-lasting target engagement, albeit exhibiting lower potencies in respect to pioglitazone. This peculiar biological profile resulted in promising antioxidant and anti-inflammatory properties, laying the ground for future developments of covalent pioglitazone derivatives.

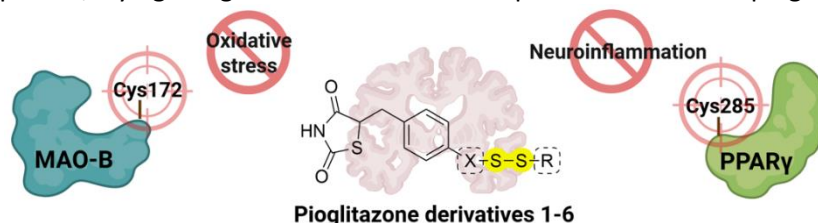


Figure 1. Drug design of new pioglitazone derivatives **1-6** as potential modulators of MAO-B and PPAR γ .

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P012

INTEGRATED MACHINE LEARNING AND STRUCTURE-BASED DISCOVERY OF TANKYRASE 1 INHIBITORS

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Tankyrase 1 (TNKS1), a key regulator of Wnt/ β -catenin signaling, represents an attractive target for anticancer drug discovery [1]. To identify TNKS1 inhibitors, we developed an integrated computational workflow combining machine learning [2], virtual screening, molecular docking, MM-GBSA refinement, molecular dynamics simulations, and experimental validation. An XGBoost classification model was trained on experimentally annotated TNKS1 inhibitors and property-matched decoys using molecular fingerprints and scaffold-based dataset partitioning. The validated model was subsequently applied to large external chemical libraries containing hundreds of thousands of compounds. AI-prioritized candidates were screened against the TNKS1 catalytic domain (Figure 1) through molecular docking, followed by MM-GBSA energetic refinement and chemical diversity analysis. The workflow identified 670 high-confidence candidates, which were clustered into 192 representative compounds. Five candidates were selected for further investigation based on consensus AI scores, docking performance, binding free energy estimates, and structural diversity. These compounds were subsequently evaluated by molecular dynamics simulations and enzymatic inhibition assays. Although most candidates showed limited experimental activity, one compound emerged as a promising TNKS1 inhibitor, displaying approximately 80% enzymatic inhibition at 0.1 μ M and maintaining stable interactions throughout molecular dynamics simulations. The agreement between computational predictions and experimental results supports the effectiveness of the proposed prioritization strategy. Overall, this study demonstrates that integrating machine learning with structure-based methodologies can efficiently reduce large chemical spaces and facilitate the identification and prioritization of TNKS1 inhibitor candidates, providing a promising framework for the discovery of potential anticancer agents.

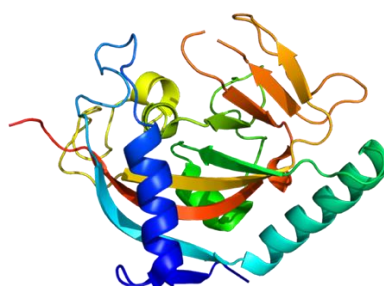


Figure 1: Crystal structure of human tankyrase 1 (PDB: 3UH4).

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P013

B.R.E.A.S.T.: AN INTERPRETABLE MACHINE LEARNING FRAMEWORK FOR PROTEOMICS-DRIVEN THERAPY OUTCOME PREDICTION IN BREAST CANCER AND TRIPLE-NEGATIVE BREAST CANCER

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Breast cancer (BC) is a highly heterogeneous disease characterized by marked molecular diversity and variable therapeutic response. Among its subtypes, Triple-Negative Breast Cancer (TNBC) is one of the most aggressive and clinically challenging, lacking targeted therapies and associated with poor prognosis. Predicting treatment outcome remains a major unmet need in precision oncology [1]. In this study, we developed B.R.E.A.S.T. (Breast cancer Enhanced AI Supported Therapy), an interpretable Artificial Intelligence (AI) framework designed to predict therapeutic response by integrating tumor proteomic profiles with clinical and treatment-related data. Proteomic data from The Cancer Genome Atlas (TCGA) [2] and The Cancer Proteome Atlas (TCPA) [3] were integrated with clinical outcomes and pharmacological annotations from the cBIOPortal [4]. Two parallel analytical settings were investigated: the full BC population and the TNBC subgroup. Thirteen supervised machine learning algorithms were benchmarked using stratified 5-fold cross-validation. Model performance was assessed using accuracy, precision, recall, F1-score, and ROC-AUC. Feature importance was evaluated through a two-step consensus ranking strategy combined with SHAP (SHapley Additive exPlanations). Differential expression between responders and non-responders was assessed using Mann–Whitney U test with FDR correction and effect size estimation (Cliff's delta) and visualized through volcano plots. Across both TCGA and TCPA BC cohorts, ensemble-based models consistently achieved the highest predictive performance, with Random Forest and ExtraTrees reaching near-perfect discrimination (ROC-AUC up to 0.998). These results were reproduced in TNBC subset, with ROC-AUC values up to 0.999 despite reduced sample size and increased biological heterogeneity, suggesting that performance is driven by biologically meaningful proteomic patterns. Learning curve analysis further mitigated overfitting risk. Feature selection identified key biomarkers mapped to key oncogenic pathways, including PI3K/AKT/mTOR signaling (e.g., AKT_pS473, RAPTOR), DNA damage response (e.g., CHK1, MRE11, PCNA), apoptosis (e.g., BCLXL), metabolism (e.g., FASN), and invasion (e.g., SNAIL, MMP14) [5]. Volcano plots revealed significant differences between responders and non-responders, with proteins such as AKT_pS473 and CHK1 enriched in non-responders [6], and RAPTOR and MRE11 associated with responder phenotypes, highlighting mechanisms related to survival signaling, DNA repair, and pathway-specific regulation of therapeutic sensitivity. Importantly, retraining models using only the top 30 features preserved high predictive performance across both cohorts, demonstrating that a parsimonious proteomic signature captures key determinants of therapeutic response. B.R.E.A.S.T. provides a robust and interpretable framework for therapy outcome prediction in TNBC, supporting the identification of clinically relevant biomarkers and advancing precision oncology strategies, particularly in aggressive subtypes such as TNBC.

Acknowledgments: Alessia Bono was supported by Fondazione Umberto Veronesi.

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P014

CATHEPSIN-B ACTIVABLE PRODRUGS OF HISTONE DEACETYLASE INHIBITORS

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Histone deacetylases (HDACs) regulate gene expression by removing acetyl groups from histones, promoting chromatin compaction and silencing tumor-suppressor genes. HDACs are often overexpressed in cancer, making HDAC inhibitors (HDACi) such as vorinostat effective therapeutic agents^[1]. However, most HDACi contain a hydroxamic acid group that contributes to systemic toxicity and poor pharmacokinetics^[2]. Cathepsin B (CTSB), a cysteine protease overexpressed in tumors and upregulated after HDAC inhibition, offers an opportunity for tumor-specific drug activation.

This project aims to design a CTSB-activated prodrug to selectively release HDAC inhibitors in tumor tissue, reducing toxicity and improving stability and specificity.^[3]

The prodrug masks the hydroxamic acid using a dual self-immolative linker with a CTSB-cleavable sequence. Upon cleavage, a CO₂-driven rearrangement triggers drug release.

Analogues were synthesized by modifying residues adjacent to proline. SPPS was accelerated using ultrasound-assisted and SUS-SPPS protocols.

In vitro assays included CTSB cleavage, stability, cytotoxicity, and Western blot analysis.

Selected candidates were evaluated in PDX models.

Prodrugs showed high stability and rapid CTSB-mediated cleavage, achieving up to 100% conversion to Vorinostat within 2 hours. Bulky side chains improved stability while maintaining enzymatic responsiveness. This CTSB-activated prodrug platform enhances tumor specificity and reduces HDACi toxicity, supporting its potential as a next-generation targeted cancer therapy.^[4]

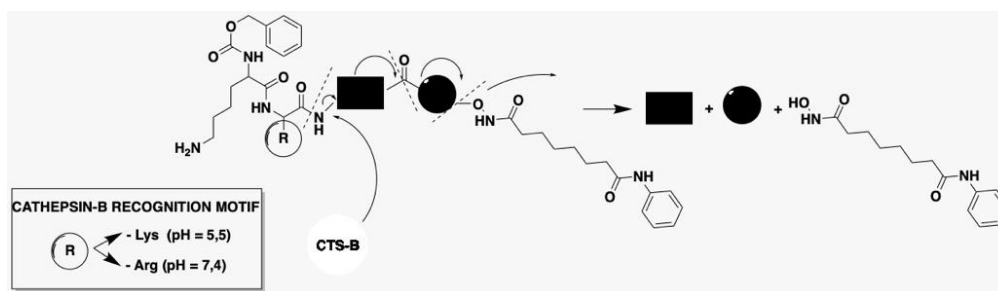


Figure 1. General mechanism of CTSB-activated HDACi prodrug

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P015

TRANSCRIPTIONAL REPRESSION OF HIV-1 VIA SMALL-MOLECULE STABILIZATION OF THE LTR-III G-QUADRUPLEX

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HIV-1 remains a major global threat because it hides inside host cell DNA, allowing it to escape the immune system. Viral transcription is heavily regulated by guanine-rich regions within the long terminal repeat (LTR) promoter, most notably the LTR-III sequence. This motif adopts a complex hybrid architecture characterized by a three-layer G-quadruplex (G4) core, a duplex-G4 junction, and an integrated duplex stem-loop [1]. Given that the formation of the LTR-III G4 promotes transcriptional silencing, small-molecule stabilization of this non-canonical structure offers a promising target for novel antiretroviral strategies. In this work, we carried out a structure-based virtual screening workflow utilizing the 10 NMR structures of LTR-III (PDB ID: 6H1K). Our computational approach was bifurcated into two distinct phases: a screening of structurally diverse compound libraries aimed at the stem-loop domain, and a focused screening of naphthalene diimide (NDI) derivatives tailored for optimized stacking with the G4-core tetrads. The most promising virtual hits from both workflows were selected for in vitro validation, where biological assays revealed several active candidates. To unravel the structural determinants underlying these results, Molecular Dynamics (MD) simulations were executed using OpenMM [2] to assess the conformational stability and persistence of the top-performing ligand-target complexes, directly supporting the link between transcriptional downregulation and the structural stabilization of the LTR-III scaffold. Based on these findings, we are currently studying novel conjugated ligands by covalently linking the optimal SLB to the highly selective NDI through tailored spacers, aiming to synthesize a single chemical entity capable of dual-site engagement. This multivalent strategy aims to increase both binding affinity and selectivity for LTR-III over background genomic DNA. This research is supported by the PRIN "Tackle HIV-1" project [3].

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National Meeting on
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17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P016

IDENTIFICATION OF NOVEL NITROGEN-BASED DERIVATIVES TARGETING SARS-CoV-2 RdRp

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Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, continues to pose a significant global health threat, with only a limited number of effective antiviral therapies currently available. The development of novel targeted antivirals remains essential, both due to the continuous emergence of viral variants capable of partially escaping vaccine-induced immunity and the potential risk of future outbreaks caused by human coronaviruses (hCoVs). To date, only a small number of compounds are known to directly interfere with viral replication. Notably, nitrogen-containing heteroaromatic scaffolds, such as nucleos(t)ide analogs, oxadiazoles, thiadiazoles, triazoles, and quinolines, have demonstrated promising antiviral activity against SARS-CoV-2 [1]. Among these, the FDA-approved drugs remdesivir and molnupiravir represent key therapeutic examples. The RNA-dependent RNA polymerase (RdRp) plays a central role in the viral replication cycle, catalyzing RNA synthesis, and is highly conserved across coronaviruses. Its essential function, combined with the absence of a human homolog, makes RdRp an attractive target for antiviral drug discovery [2]. Inhibitors of this enzyme are particularly appealing due to their potential broad-spectrum activity and higher barrier to resistance. In this context, our work focuses on the identification of novel heterocyclic small molecules targeting SARS-CoV-2 RdRp. Building on our expertise in the design and synthesis of antiviral agents [3,4], we identified new heterocyclic derivatives as promising hit compounds. A ligand-based approach was employed to identify, design and optimize these molecules, leading to improved potency against this enzymatic target. Furthermore, molecular docking studies were performed to elucidate key interactions within the catalytic site of RdRp. The results of biological evaluations will be presented and discussed.

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P017

GRIPkit: A COMPREHENSIVE COMPUTATIONAL SUITE FOR THE CHARACTERIZATION AND QUANTIFICATION OF NON-COVALENT INTERACTIONS IN PROTEIN-LIGAND COMPLEXES

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Non-covalent interactions (NCIs) govern molecular recognition and binding affinity, yet they are often reduced to coarse, empirical terms in computational drug-discovery workflows. We present GRIPkit, a comprehensive computational suite for the characterization and quantification of NCIs in protein-ligand complexes, built on two integrated modules: GRIPProfiler (heuristic geometric profiling) and GRIPqm (physics-based characterization).

GRIPProfiler is a consensus profiling framework integrating complementary state-of-the-art tools (e.g., PLIP [1], ProLIF [2], BINANA [3]) that detects, classifies, and merges NCIs from 3D binding site structures into a unified, deeply annotated dataset, with efficient, parallelized scaling to large structure datasets.

GRIPqm is an automated quantum-mechanics workflow for the physics-based characterization of NCIs, built on both GPU- and CPU-based engines (GPU4PySCF [4], ORCA [5]). It comprises DFT calculation of the electron density of the ligand-binding-site clusters, an ensemble of methods for electron-density analysis (e.g., Multiwfn [6]), and the DFT-based quantification of local fragment-fragment interaction energies.

GRIPkit adopts a dual architecture: a core Python library optimized for parallelized, high-throughput screening and workflow integration, and a standalone Graphical User Interface (GUI) for non-programming users that exposes all GRIPkit modules and provides interactive 2D/3D visualization of single- and multi-complex analysis results. GRIPkit serves multiple purposes in computational drug discovery: as a physics-informed component to guide generative artificial intelligence models; as an efficient filtering and ranking tool to prioritize large candidate sets of molecular docking/co-folding poses; and as a stand-alone, intuitive GUI profiler for structural interaction analysis.

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P018

PHENOTHIAZINE DERIVATIVES ENDOWED WITH ANTIOXIDANT ACTIVITY AS MULTIFUNCTIONAL COMPOUNDS IN NEURODEGENERATIVE DISEASE

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Oxidative stress represents a critical, nonspecific pathological process underlying numerous diseases. Among these, Alzheimer’s disease (AD) stands out as a neurodegenerative disorder driven by the interplay of multifaced factors including amyloid plaque deposition, neurofibrillary tangle formation, cholinergic insufficiency, excitotoxicity, and neuroinflammation. Despite substantial progress in unraveling AD pathogenesis, current therapeutic strategies are predominantly symptomatic and fail to arrest disease progression. Several evidence highlights the pivotal role of oxidative stress in AD pathology, rendering it a major target for drug development [1]. Given this pathological complexity, there is growing interest in designing the so-called multi-target directed ligands (MTDLs), compounds capable of simultaneously modulating different pathological pathways involved in the disease [2]. Phenothiazine derivatives represent a prominent class of heterocyclic compounds possessing a broad spectrum of pharmacological activities. Their antioxidant properties have attracted considerable interest due to potential therapeutic applications in mitigating oxidative stress-related diseases. Furthermore, the structural versatility of the phenothiazine core allows the introduction of different pharmacophoric moieties able to enhance affinity toward acetylcholinesterase and butyrylcholinesterase, and other relevant molecular targets, making these compounds particularly attractive for multitarget therapeutic approaches [3]. In this context, the present work focuses on the design and biological evaluation of novel phenothiazine-based derivatives (Figure 1) developed as multifunctional agents combining antioxidant properties with inhibitory activity toward key AD targets such as acetylcholinesterase and butyrylcholinesterase. A molecular docking study was performed to rationalize the biological outcomes and elucidate the binding modes within the target enzymes.

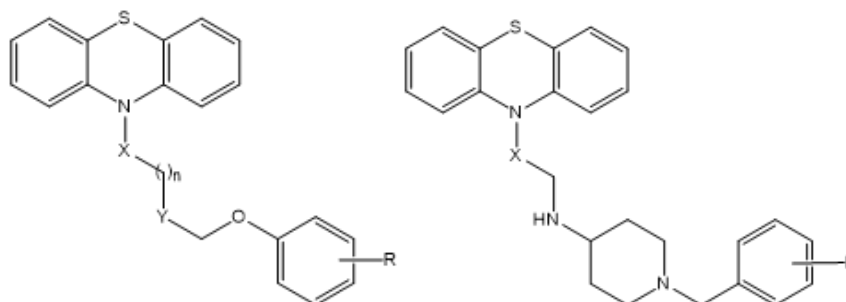


Figure 1. General structures for phenothiazine derivatives

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P019

FROM POMEGRANATE JUICE TO BIOACTIVE EXTRACTS: PROCESSING-DEPENDENT PHYTOCHEMICAL MODULATION AND NEUROPROTECTIVE POTENTIAL OF RELATED NUTRACEUTICALS

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Pomegranate-derived nutraceuticals are increasingly attracting scientific interest due to their high content of polyphenols, ellagitannins, anthocyanins, and antioxidant metabolites involved in the modulation of oxidative stress and neuroinflammatory pathways. In this contribution, we combined phytochemical, bio-toxicological, in vivo, and computational evidence obtained from complementary studies on pomegranate juices and derived extracts in order to evaluate how processing technologies and phytochemical composition influence nutraceutical efficacy and neuroprotective potential in vitro and in vivo. Advanced analytical characterization of differently processed pomegranate juices demonstrated that industrial treatment strongly affects the preservation of bioactive compounds. Comparative analyses between thermally pasteurized juice (PJ) and high-pressure processed juice (HP) revealed substantial differences in phytochemical profiles, antioxidant activity, and biological properties. HPLC-DAD, DI-ESI-MS/MS, and NMR analyses identified punicalins, punicalagins, ellagic acid derivatives, anthocyanins, vitamin C, organic acids, amino acids, and sugars as major constituents. HP processing better preserved anthocyanins, whereas pasteurization retained higher levels of ellagitannins, vitamin C, total phenolics, and antioxidant activity. In particular, PJ showed significantly higher DPPH, ABTS, FRAP, CUPRAC, and metal-chelating activities, together with stronger tyrosinase inhibitory effects. Both juices exhibited low ecotoxicological impact and acceptable biocompatibility profiles in brine shrimp and allelopathy assays, supporting their suitability for nutraceutical development [1].

The second experimental approach investigated pomegranate juice extracts in an adult zebrafish model of aluminum chloride and lead acetate-induced neurotoxicity. Treatment with pomegranate extracts significantly attenuated anxiety-like behavior, memory impairment, oxidative stress, lipid peroxidation, and cholinergic dysregulation induced by heavy metals. The extracts restored endogenous antioxidant defenses, including superoxide dismutase, catalase, glutathione peroxidase, and glutathione levels, while reducing malondialdehyde accumulation and protein oxidation. Complementary in silico analyses further supported the nutraceutical potential of representative pomegranate metabolites, including ellagic acid derivatives, anthocyanins, and urolithin-related compounds. ADME/Tox prediction, PASS analysis, and target interaction modeling suggested favorable pharmacokinetic properties and multitarget neuroprotective activity associated with antioxidant modulation, cholinesterase interaction, and cellular redox regulation. Overall, these findings demonstrate that pomegranate juices and derived extracts act as multitarget nutraceutical systems whose efficacy is highly dependent on processing technologies and extraction methods. These results provide a translational framework for the development of standardized pomegranate-based nutraceutical formulations with optimized stability, safety, and biological activity for applications in oxidative stress-related and neurodegenerative conditions.

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P020

COUMARIN- AND DIPICOLYLAMINE-TERPENOID HYBRIDS AS SELECTIVE CARBONIC ANHYDRASES IX AND XII INHIBITORS: MECHANISTIC IN-SIGHTS AND SELECTIVE ANTI-MYELOMA POTENTIAL

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Among cancers, multiple myeloma (MM) is a plasma cell malignancy sustained by hypoxia-driven metabolic adaptation, extracellular acidification, and redox imbalance. Tight regulation of tumor extracellular pH, mediated by Carbonic Anhydrases (CAs) IX and XII, is crucial for myeloma survival, progression, and stemness, making these isoforms attractive therapeutic targets. We designed and synthesized a library of terpenoid-based hybrids by derivatizing chlorothymol and 4-isopropyl-3-methylphenol with either the natural coumarin umbelliferon or the 2,2'-dipicolylamine (DPA) scaffold. This chemical strategy aimed to selectively inhibit tumor-associated CAs IX/XII through coumarin- or DPA-mediated recognition, while terpenoid fragments were introduced to enhance lipophilicity, membrane permeability, and potential redox-modulating properties. The compounds were tested by a Stopped-Flow assay for CA inhibition, in cell-based assays for antiproliferative properties and by means of several antioxidant assays. The most active compounds, connecting the coumarin core to a terpenoid tail, inhibited the targeted CAs in the nanomolar range, showing higher selectivity over off-target isoforms (I and II). In studies performed on MM cell lines, selected derivatives reduced viability ($IC_{50} = 15.8\text{--}85.4\text{ }\mu\text{M}$) and displayed favorable selectivity over normal cells. In silico investigations suggested that the compounds were able to interact selectively with the target enzymes. Collectively, these results support a dual-targeting strategy in which selective inhibition of tumor-associated CAs, combined with redox modulation, interferes with adaptive mechanisms of MM cells, providing a rational framework for the development of multifunctional agents against metabolically resilient hematological malignancies (Figure 1) [1].

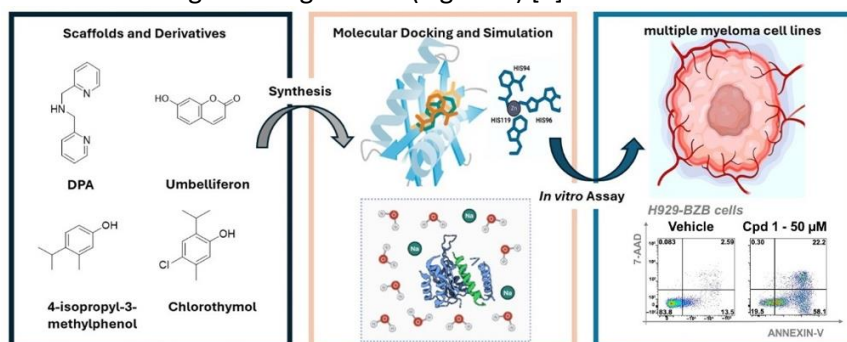


Figure 1.

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P021

DISCOVERY OF SELECTIVE MALAT1 TRIPLE HELIX LIGANDS THROUGH INTEGRATED BIOCHEMICAL SCREENING

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Long non-coding RNAs (lncRNAs) have emerged as promising therapeutic targets due to their central roles in gene regulation and cancer progression. Among them, the lncRNA MALAT1 contains a highly conserved triple-helical structure at its 3' end that is essential for transcript stability, making it an attractive target for small-molecule intervention.^[1] Despite its therapeutic potential, the identification of ligands capable of selectively recognizing and modulating RNA tertiary structures remains a major challenge. Here, we report the discovery of selective small-molecule ligands that target the MALAT1 triple helix. This was achieved using an integrated biochemical screening strategy applied to a focused compound library.^[2] This approach led to the identification of two active molecules, **DV095** and **DV153**, which bind the MALAT1 RNA with high affinity ($K_d = 0.08 \pm 0.02 \mu\text{M}$ and $0.05 \pm 0.06 \mu\text{M}$, respectively) and induce destabilization of the triple-helical structure (**Figure 1**). Their binding mode was further characterized by orthogonal assays, including fluorescence intercalator displacement experiments and binding studies against DNA and tRNA controls, demonstrating a selective, non-intercalative interaction with the target RNA. Overall, these findings provide valuable chemical tools for investigating the biological function of the MALAT1 triple helix and demonstrate the feasibility of selectively targeting RNA tertiary structures with small molecules. This work further supports the development of innovative RNA-targeted therapeutic strategies.

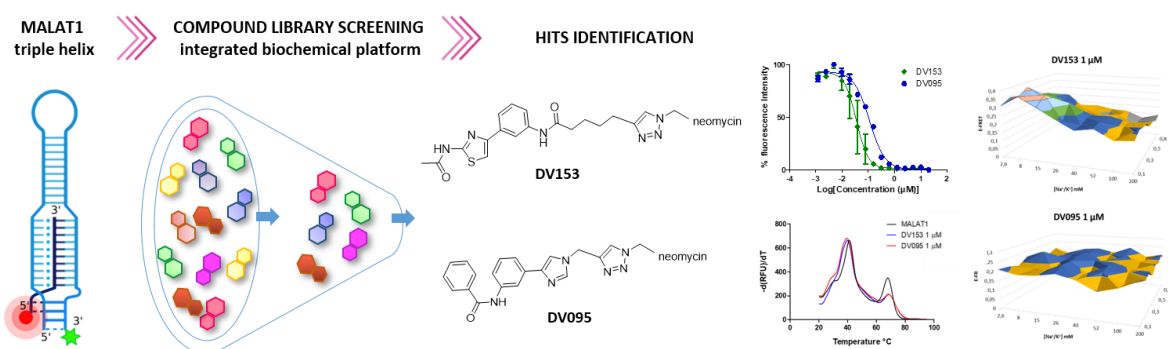


Figure 1: Schematic representation of the experimental workflow.

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P022

COMPUTATIONAL AND KINETIC ANALYSIS OF PSMA RADIOLIGANDS TO PREDICT *IN VIVO* KINETIC PROFILE

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Prostate-Specific Membrane Antigen (PSMA) is a zinc-metalloproteinase overexpressed in prostate cancer cells and is a key target for imaging and therapy [1,2]. Among clinically used PSMA radioligands, [⁶⁸Ga]Ga-PSMA-11 and the fluorinated tracers [¹⁸F]PSMA-1007, [¹⁸F]DCFPyL, and [¹⁸F]JK-PSMA-7 show pharmacokinetic differences that are not yet fully understood. Here, we investigate their binding mechanisms by combining *in silico* analyses of ligand-target interactions with *in vitro* kinetic measurements of association (K_{on}) and dissociation (K_{off}) rates.

Molecular dynamics simulations using the PSMA crystal structure (PDB ID: 3D7H, 800 ns) revealed distinct binding modes for all radioligands. Ligand stabilization is mainly determined by interactions with the Entrance Lid (Trp541–Gly548) and the Arene-Binding Site (ABS) (Arg463, Arg511, and Trp541) [3]. MMPBSA calculations showed moderate differences in binding free energy (ΔG) values, with [¹⁸F]PSMA-1007 exhibiting the lowest ΔG (−88.68 kcal/mol) and thus emerging as the most stable bound ligand. Notably, it was the only ligand able to consistently reach and stabilize the ABS. In contrast, [¹⁸F]DCFPyL (ΔG −65.43 kcal/mol) and [¹⁸F]JK-PSMA-7 (ΔG −64.60 kcal/mol) primarily interact with the Arginine Patch (Arg534, Arg536, Arg463), while [⁶⁸Ga]Ga-PSMA-11 (ΔG −55.48 kcal/mol) remained more solvent-exposed within the upper region of the Entrance Funnel.

In vitro kinetic assays on PC3-PIP cells were in agreement with the computational findings, although affinities were comparable, dissociation kinetics differed markedly. [¹⁸F]PSMA-1007 displayed the slowest dissociation rate, followed by [¹⁸F]DCFPyL and [¹⁸F]JK-PSMA-7, whereas [⁶⁸Ga]Ga-PSMA-11 dissociated the fastest. The computational data suggest that ligand retention depends on specific structural interactions with the target. In particular, our results indicate that engagement of [¹⁸F]PSMA-1007 with the ABS creates a high dissociation barrier, leading to prolonged residence time and near-irreversible binding under experimental conditions [4]. Overall, this combined approach provides valuable insights for predicting PSMA-binding behaviour and kinetics, aiding the rational design of novel PSMA radiopharmaceuticals for diagnostic and therapeutic applications.

Acknowledgements: This work benefited from services and resources provided by the EGI Federation, thanks to CESNET-MCC and e-INFRA CZ project (ID:90254), supported by the Ministry of Education, Youth and Sports of the Czech Republic.

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P023

COMPUTATIONAL DISCOVERY OF DUAL HUMAN AND MUSHROOM TYROSINASE INHIBITORS
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Tyrosinase (TYR) is a copper-containing oxidase that catalysed two key reactions in the biosynthesis of melanin. It plays a pivotal role in the development of hyperpigmentation disorders, so the inhibition of TYR activity represents the main mechanism of action for skin-whitening agents [1].

Although several TYR inhibitors are currently available on the market, their therapeutic application is often limited by the occurrence of adverse effects [2]. In this context, natural compounds represent a particularly attractive source of novel TYR inhibitors, owing to their structural diversity and generally favourable safety profile.

Testing the inhibitory activity of compounds against TYR from *Agaricus bisporus* (AbTYR) has long been a common practice for identifying potential therapeutics from both synthetic and natural sources. However, the structural divergence between human tyrosinase (hTYR) and AbTYR poses a significant challenge in the development of therapeutically effective drugs. The application of machine learning techniques enabled the prediction of compound activity exclusively against AbTYR, due to the large number of inhibitors with known activity available for training and validating the predictive protocol. The optimal protocol was identified as the combination of the Morgan fingerprint and the k-NN algorithm [3].

Starting on this framework, a machine learning-based protocol was initially employed as a preliminary filtering strategy to predict inhibitory activity against AbTYR. A first virtual screening campaign was conducted on the MolPort Natural Compounds Database, and compounds predicted as active by the model were subsequently subjected to a second virtual screening step to evaluate their potential activity against hTYR. At this stage, a pharmacophore model was used as a screening filter, generated from the docking pose of Meht3, a hTYR inhibitor previously identified in our laboratory [4-5]. Compounds matching the pharmacophoric features and complying with Lipinski's rule of five were selected for further investigation using conventional computational approaches. Molecular docking studies were then performed, and compounds exhibiting binding modes comparable to that of Meht3 were prioritized for advanced computational analyses, including molecular dynamics simulations and ADMET profiling.

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P024

MOLECULAR DOCKING OF ANTI-MELANOGENIC AND FLUORESCENT NATURAL PRODUCT-INSPIRED DERIVATIVES AFFECTING TYROSINASE ACTIVITY

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Curcumin, the major polyphenolic constituent of *Curcuma longa*, has attracted considerable interest in its antioxidant, anti-inflammatory, and anti-melanogenic properties [1]. In this project, curcumin was employed as a natural molecular platform for the synthesis of two derivatives (**1** and **2**). These compounds were synthesized by coupling curcumin with the known tyrosinase inhibitor 4-(piperazin-1-yl)phenol [2], employing structurally diverse linkers (Figure 1A). They were designed to combine the intrinsic biological activity and fluorescence of the natural scaffold with enhanced tyrosinase inhibition and potential imaging capability. Both derivatives were synthesized and evaluated against tyrosinase from *Agaricus bisporus* (AbTYR), revealing improved inhibitory potency compared with curcumin. Kinetic studies were performed to investigate their inhibitory mechanism.

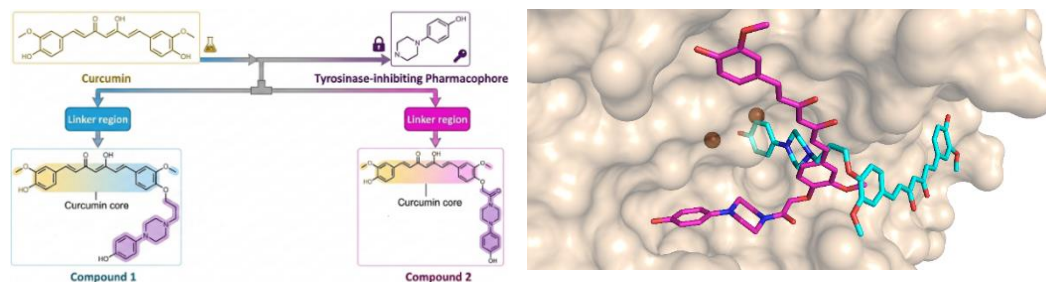


Figure 2: A) Conjugation of the curcumin fragment with the pharmacophore leading to **Compounds 1** and **2**. B) 3D representation of the molecular docking studies of **Compound 1** (cyan) and **2** (magenta) within the AbTYR active site

Docking simulation using the crystal structure of AbTYR [3] (Figure 1B) revealed distinct binding modes driven by the linker structure: compound **1** oriented toward the catalytic site, in which the phenolic pharmacophore engaged the copper-containing active site via π - π stacking and hydrophobic contacts. In contrast, compound **2** assumed a markedly different orientation, stabilized by a network of hydrophobic interactions, hydrogen bonds and aromatic contacts. The biological relevance was further confirmed *in vivo* using zebrafish embryos; in particular, compound **2** exhibited a significant depigmenting action and fluorescence microscopy demonstrated that **1** selectively accumulated in B16 melanoma cells, producing intense intracellular fluorescence not observed with curcumin alone or in non-melanogenic cell lines.

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P025

EVALUATION OF THE ANTITUMOR ACTIVITY OF THE AYURVEDIC MIXTURE TRIPHALA

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The word "Ayurveda" derives from the Sanskrit terms *Ayu* (life) and *Veda* (knowledge/science), translating to "the science of life." This ancient traditional Indian medicine focuses on maintaining harmony between body, mind and spirit, heavily relying on the individual's natural constitution for diagnosis and treatment. Ayurvedic healthcare employs a multifaceted approach that integrates personalized dietary guidelines, mineral-based formulations, and polyherbal mixtures. A great example of ayurvedic polyherbal formulation is Triphala ("three fruits"), composed by three Indian fruits Haritaki (*T. chebula*), Amalaki (*E. officinalis*) and Bibhitaki (*T. bellerica*). While traditionally used for millennia to treat gastrointestinal disorders, Triphala is gaining significant scientific attention for its pleiotropic potential. Indeed, several studies have demonstrated its diverse biological properties, including promising antitumor activity, largely driven by its high content of tannins and polyphenols [1]. Given that breast cancer remains the leading cause of cancer-related mortality in women globally [2,3], developing novel therapeutic strategies is urgent. In this context, natural compounds offer a promising avenue due to their efficacy and reduced systemic toxicity. To this end, the *in vitro* anti-breast cancer activity of Triphala has been assessed. Triphala exhibited a potent and selective anticancer effect in triple-negative breast cancer cells MDA-MB-231, with no significant cytotoxicity on the normal epithelial mammary MCF-10A cells. This cytotoxic activity was driven by extensive genomic DNA fragmentation. Additionally, Triphala significantly inhibited cancer cell migration, interfering with the actin cytoskeleton dynamics. Indeed, Triphala disrupted β -actin filament organization, directly inhibiting actin polymerization and promoting filament depolymerization with an efficacy comparable to Latrunculin A.



Figure 1. Triphala powder (*Churna*) and its constituent fruits.

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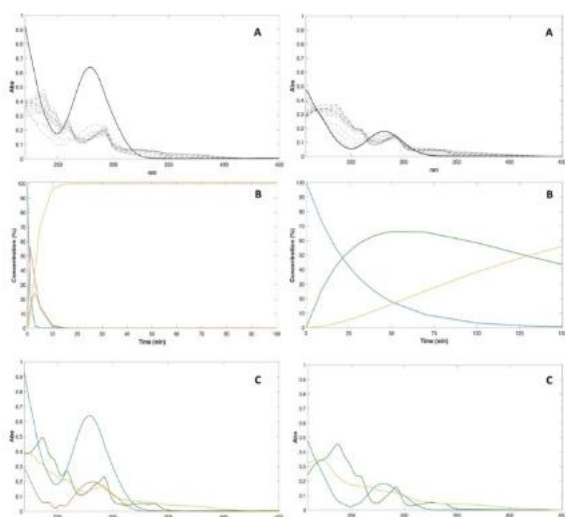
P026

DEVELOPMENT OF LIGHT-STABLE DICLOFENAC SODIUM CARRIERS THROUGH A SUSTAINABLE MEMBRANE-BASED APPROACH

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Diclofenac sodium (DS) is highly sensitive to environmental stressors, including light, temperature and humidity which often degrade the drug in liquid formulations. To protect drug from stressing conditions, this study investigates the use of membrane nanoprecipitation (MN) as a high-yield, efficient strategy for creating solid lipid nanoparticles (SLNs) using a natural cocoa butter matrix [1]. The experimental phase involved a direct comparison between MN and traditional batch nanoprecipitation techniques, adjusting various processing and chemical variables to refine the resulting SLNs. Chemical characterization of the proposed formulation was performed by DSC and FTIR analyses. The findings indicate that the MN system is capable of generating nanoparticles with a mean

diameter of 421 ± 14 nm. When an acetate buffer at pH 4.1 was employed as the non-solvent medium, the process achieved an exceptional encapsulation efficiency of $95 \pm 3.2\%$ and a drug loading of $8.8 \pm 0.2\%$. The efficacy of SLNs in preserving DS stability was investigated under simulated sunlight exposure. Photodegradation experiments were made according to the International Conference on Harmonization rules [2], while photodegradation kinetics was calculated by using chemometric methods. Multivariate Curve Resolution-Alternating Least Squares was selected for its ability in estimating the pure spectra and the concentration (time) profiles of the drug and relative photoproducts [3]. A residual drug concentration of 90% was reached after 3.34 min, whereas the aqueous solution reached the same residual concentration after only 0.072 min. Figure 1 shows the absorbance spectra (A) of DS aqueous solution and DS-loaded SLNs, concentration profiles of DS and photoproducts (B) and relative absorbance spectra from MCR elaboration when prepared in solution and in SLNs (C). Accordingly, MN method provides a green, continuous, and scalable manufacturing platform for producing pharmaceutical delivery systems that successfully shield light-sensitive drugs from rapid degradation.

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P027

PYRAZOLYL-THIOUREA DERIVATIVES AS SIRT2 INHIBITORS: STRUCTURAL DIVERSIFICATION AND SAR STUDIES

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Sirtuins (SIRT1–7) are NAD⁺-dependent deacetylases that play crucial roles in multiple cellular processes, and their dysregulation has been strongly associated with neurodegenerative disorders and cancer [1]. Among them, SIRT2 has attracted particular attention due to its involvement in cell cycle regulation, cytoskeletal dynamics via α -tubulin deacetylation, and tumor progression. The pharmaceutical potential of SIRT2 is further supported by its implication in neurodegenerative diseases [2].

In this context, a series of pyrazolyl–thiourea derivatives (PTUs) **1** (Figure 1) has emerged as a promising class of SIRT2 inhibitors, exhibiting selective antiproliferative activity against HepG2 cells while maintaining low toxicity toward normal fibroblasts [3]. To further extend structure–activity relationships (SARs) on PTUs **1**, a novel series of derivatives was designed and synthesized. PTUs **2** and **3** (Figure 1) shared with the lead derivatives **1** the thiourea moiety at position 4 of the pyrazole core and were differently decorated on the heterocyclic core.

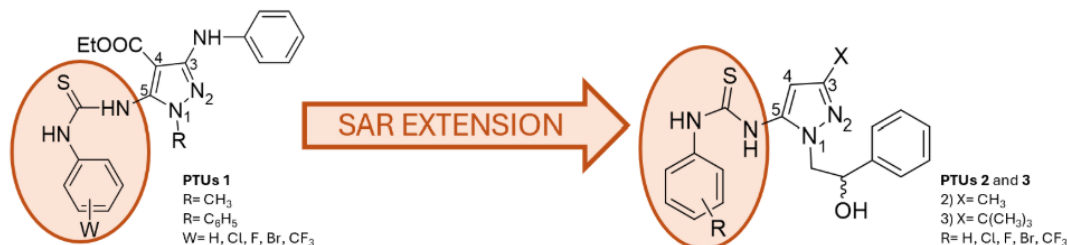


Figure 1: Structure of previous derivatives **1** and new functionalized compounds **2** and **3**.

In detail: i) at the C3 position, the original N-phenyl group was replaced with small alkyl substituents (e.g., methyl or tert-butyl) to modulate steric hindrance, conformational flexibility, and lipophilicity; ii) at the N1 position a (±)2-hydroxyphenylethyl side chain was introduced to enhance hydrogen-bonding interactions and fine-tuning the electronic properties of the system. The SIRT2 inhibition and the cytotoxic properties of novel PTUs **2** and **3** were assessed on isolated enzyme and cell-based models, respectively. Selected member of the series proved to inhibit SIRT2 at micromolar concentrations and evidenced a selective/promising antiproliferative activity. Furthermore, computational studies were carried out to identify the molecular determinant for the interaction between the novel PTUs and SIRT2. Synthetic approaches, biological data, and molecular docking studies will be presented and discussed in the poster.

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P028

A NOVEL INDOLE-BASED MULTI-TARGET THERAPEUTIC AGENT TARGETING hCA IX/XII, WNT/ β -CATENIN PATHWAY, AND P-gp

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Human carbonic anhydrase (hCA) is a ubiquitous enzyme implicated in physiological functions, such as pH and CO₂ homeostasis. However, deregulation of this pivotal protein is involved in various pathologies.^[1] In many tumors like glioblastoma, colorectal cancer and breast cancer, hCA IX and XII isoforms are particularly overexpressed. Hence, the interest in the selective modulation of these targets for their potential therapeutic use. Based on differences in the cavity volumes of a portion of the catalytic core of hCA I, II, IX, and XII isoforms, a new series of pyrrole- and indole-based molecules (**2-13**) was designed with the aim of increasing selectivity towards isoforms IX and XII with small group introduction, while maintaining the valuable inhibition of Wnt/ β -catenin signaling pathway and P-glycoprotein (P-gp) of **1** (Figure 1).^[2] Compound **12** exhibited the most promising pharmacological profile. The compound potently inhibited hCA IX and XII with K_i values of 5.8 nM and 7.8 nM, respectively, showing markedly improved selectivity over hCA I and II. Compound **12** significantly inhibited Wnt/ β -catenin signaling by suppressing TOPFlash transcriptional activity and reducing MYC, FGF20, and SALL4 expression. Furthermore, it disrupted the β -catenin/TCF-4 interaction, impairing oncogenic transcriptional activation. In multidrug-resistant HT29/DX and MDCK/P-gp cells, compound **12** restored doxorubicin sensitivity and increased intracellular drug accumulation, confirming functional inhibition of P-gp.

A polypharmacological strategy may provide a more effective therapeutic approach owing to its cumulative action on multiple targets, making it useful for multifactorial diseases such as cancer, where numerous pathways are involved. Among the new series, compound **12** resulted a promising candidate for further development as an antitumor agent.

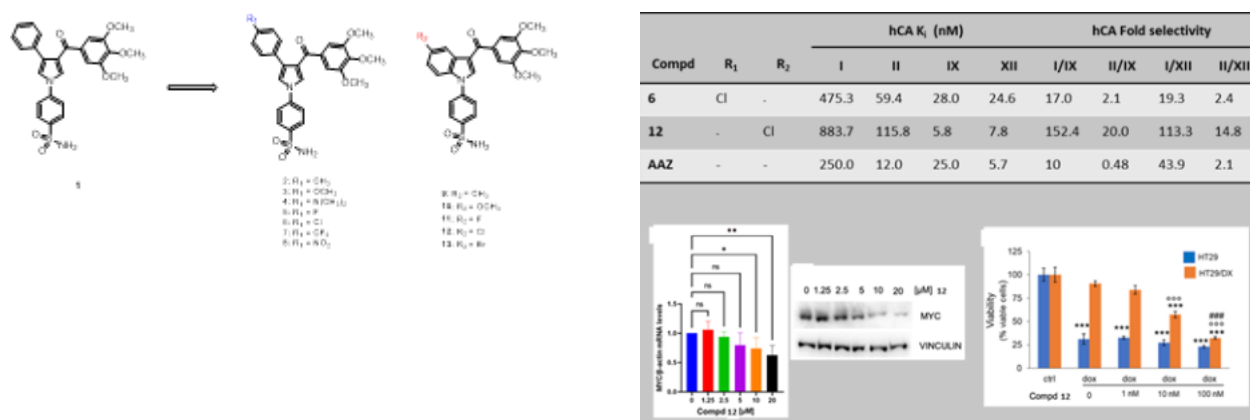


Figure 1. Structure of compounds 1-13 and biological activity of compounds 6 and 12.

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P029

NEW CB2 DUALSTERIC LIGANDS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a chronic inflammatory disorder characterized by demyelination, axonal damage and progressive neurodegeneration; neuropathic pain is a frequent, highly disabling symptom that is often poorly controlled by current therapies. Increased CB2-immunoreactive microglia in MS patients suggests CB2 modulation as a promising and safe therapeutic approach. [1] We report the design and synthesis of novel dualsteric CB2 modulators obtained by molecular hybridization of the selective CB2 agonist COR167 with cannabidiol (CBD) or simplified resorcinolic analogues. Hybrids incorporate variable linkers (length and heteroatom content) intended to permit simultaneous engagement of orthosteric and allosteric receptor sites (Figure 1).

Compounds were profiled *in vitro* for cytotoxicity and anti-inflammatory effects on BV2 murine microglia, with complementary neuronal assays providing preliminary neuroprotection data. Some resorcinol-bearing hybrids and molecules featuring elongated or heteroatom-containing linkers showed relatively enhanced activity, whereas others exhibited limited protective effects. Of note, COR1883 displayed the best neuroprotective profile with properties suggesting the potential involvement of different receptors.

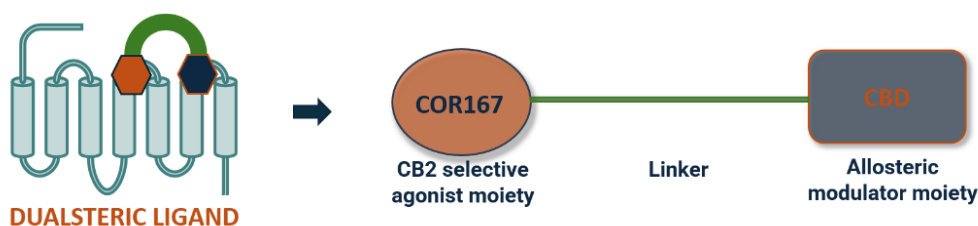


Figure 1. Schematic representation of the dualsteric compounds.

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P030

DISCOVERY OF A SELECTIVE INDOLE-BASED *L*TR INHIBITOR FOR ANTI-LEISHMANIA THERAPY THROUGH A ONE HEALTH-GUIDED MULTISCALE COMPUTATIONAL FRAMEWORK

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Leishmaniasis remains a major global health concern, exacerbated by the limited availability of safe, effective, and selective therapeutic options. Among the most extensively validated molecular targets in trypanosomatid parasites is trypanothione reductase (TR), a flavoenzyme essential for maintaining intracellular redox homeostasis and parasite survival [1]. Here, we report a multiscale computational strategy to identify selective inhibitors of *Leishmania infantum* trypanothione reductase (*L*TR). A structure-based virtual screening (SBVS) campaign identified a natural indole-based compound as a promising hit. To further characterize ligand recognition and binding determinants, molecular dynamics (MD) simulations were integrated with binding free-energy approaches, including MM-GBSA and free-energy perturbation (FEP) calculations, thereby enabling detailed investigation of ligand stability, binding energetics, and structure–activity relationships (SAR). Computational analyses revealed that the lead compound stably occupies the *L*TR catalytic cavity, engaging in both the NADPH-binding region and the adjacent door-stop pocket. Experimental validation confirmed inhibition of *L*TR in the micromolar range, with approximately 9-fold selectivity over human glutathione reductase, in agreement with computational predictions. Furthermore, the compound displayed antiparasitic activity against the promastigote stage of *Leishmania* while showing no significant cytotoxicity toward human macrophages and monocytes, supporting a favorable preliminary safety profile within a One Health perspective. Consistent with these findings, machine learning–based toxicity predictions did not indicate major liabilities related to ecotoxicity or nutritional toxicity.

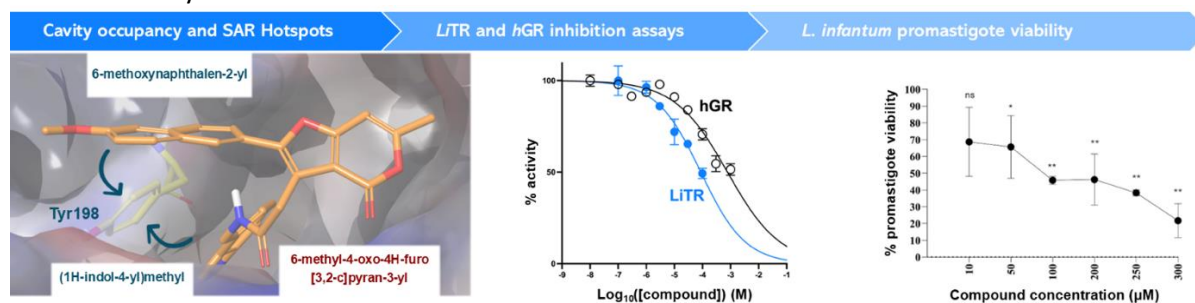


Figure 1. Identification and validation of selective indole-based scaffold targeting *L*TR for anti-leishmanial therapy.

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XXX

National Meeting on
Medicinal Chemistry

Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P031

TOWARDS A COMPREHENSIVE DE NOVO DESIGN APPROACH: THE DISCOVERY OF P38:MK2
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Modern drug discovery must contend with still many challenges including a fast-moving competitive landscape, high development costs, and low project success rates. Schrödinger's computational platform addresses these challenges, leveraging physics-based methods and AI/ML workflows to accelerate DMTA cycles.

Schrödinger's de novo design approach utilizes AutoDesigner [1,2] for ultra-large scale chemical space exploration, generating and prioritizing billions of novel structures. This is combined with rigorous free energy calculations using FEP+ [3,4] in an iterative fashion (Active Learning FEP+) to rapidly score libraries and prioritize design ideas with optimal potency. Here, we show the successful application of this integrated workflow in the discovery of p38:MK2 molecular glues, enabling systematic scaffold and R-group exploration and leading to potent and selective hits that showed pronounced TNF α reduction in in vivo models. The integrated use of Generative ML is also effectively shown on the same project where, combined with Autodesigner and the predictive power of Active Learning FEP+, rapidly leads to the generation of novel molecules that are optimized not only for potency but also for other project endpoints. To promote the design of molecules that can be easily synthesized, we describe a novel retrosynthesis method, RetroSynth, that deconstructs complex target molecules into commercially available starting materials, prioritizing cost-efficient synthetic routes and leveraging existing project chemistry. Internal validation shows RetroSynth significantly outperforms alternative solutions in terms of accuracy and real-world drug discovery projects feasibility.

Altogether, the presented tools compose a fully-integrated, comprehensive de novo design workflow that efficiently generates synthetically tractable ideas that satisfy project requirements, ultimately accelerating lead optimization.

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P032

STRUCTURE-ACTIVITY OF β -LACTAM AND β -LACTAMASE INHIBITOR COMBINATIONS: ASSESSING THE IMPACT OF AMOXICILLIN SHORTAGES IN ITALY (2020–2024)

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Amoxicillin and clavulanic acid form a classic synergistic combination within β -lactam therapy. Categorized under the WHO AWaRe "Access" group to promote optimal use and combat antimicrobial resistance (AMR), amoxicillin acts as a bactericidal agent targeting penicillin-binding proteins (PBPs) to inhibit peptidoglycan cross-linking, while clavulanic acid functions as a suicidal, mechanism-based inhibitor of β -lactamase enzymes.^[1]

This study provides a comprehensive evaluation of the structural and pharmacodynamic relationship of β -lactam antibiotics, focusing on amoxicillin/clavulanic acid utilization patterns in Italy over the 2020–2024 period. Specifically, it assesses the impact on clinical practice across geographical regions and distribution channels, focusing on how structural shifts influence resistance profiles.

Retrospective structural and therapeutic analyses were performed utilizing national pharmaceutical prescription databases (2020-2024).^[2] Standardized metrics evaluated included consumption intensity measured in Defined Daily Doses per 1,000 inhabitants per day (DDD/1,000 ind/die) to trace shifts in drug exposure. Comparative regional evaluations analyzed the proportion of β -lactamase inhibitor combinations relative to total β -lactam utilization.

Daily dosage usage of β -lactam antibiotics increased post-pandemic, rising from 17.1 DDD/1,000 ind/die in 2021 to a peak of 22.4 in 2023, before stabilizing around 18.0 in 2024.^[3-6] Regional analyses revealed persistent disparities: Southern regions consistently maintained the highest consumption rate of amoxicillin/clavulanic acid (19.2 DDD/1,000 ind/die in 2024) compared to Central (18.4) and Northern regions (14.6).

Market shortages of narrow-spectrum amoxicillin accelerate a shift toward amoxicillin/clavulanic acid, driving unnecessary broad-spectrum coverage and increasing the risk of enzymatic resistance evolution. Mitigating these biochemical and clinical challenges requires optimizing co-formulation ratios, preserving active core structures, and restoring balance to PBP-targeted monotherapies to safeguard core β -lactams against emerging resistance mechanisms.

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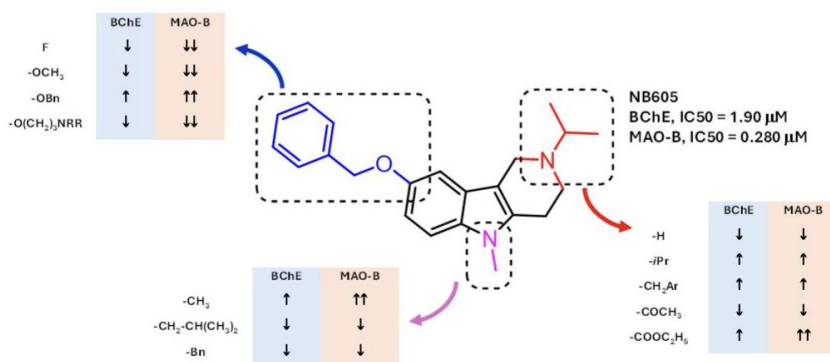
P033

INVESTIGATING SARs OF NOVEL 8-BENZYLOXY- γ -CARBOLINE DERIVATIVES AS MULTITARGET-DIRECTED LIGANDS FOR NEURODEGENERATIVE DISEASES

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Despite the progresses in understanding of the multifactorial nature of Alzheimer's disease (AD), the overall pathological mechanism underlying the disease has not been completely understood, and efforts to develop effective disease-modifying drugs largely failed [1]. A promising strategy to disclose new agents against AD is based on the design and optimization of multitarget-directed ligands (MTDLs) [2]. Carbolines, owing to their broad spectrum of biological activities, are nature-inspired privileged scaffolds in medicinal chemistry, on the other hand investigated for the treatment of neurodegenerative disorders [3]. We recently reported diverse indole-fused tricycles emerging as interesting molecular scaffolds of novel compounds endowed with neuroprotective activities [4,5]. Herein, aiming to gain new insights into the γ -carbolines' neuropharmacological potential, two series of 1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole (THPI) derivatives were designed, synthesized and tested. Among them, several 8-benzyloxy substituted γ -carbolines exhibited promising inhibitory activity toward two AD-related drug targets, namely butyrylcholinesterase (BChE) and monoamine oxidase B (MAO B). In-silico studies, including molecular docking analyses, highlighted favorable interactions within the catalytic active sites of the investigated enzymes and help interpretation of the structure-activity relationships (SARs).



Furthermore, the most active γ -carboline derivatives showed suitable drug-likeness properties (stability in plasma serum and S9 fraction, PAMPA permeation, and HSA affinity).

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P034

DEVELOPMENT OF NOVEL CHALCONE DERIVATIVES: DESIGN, SYNTHESIS AND ANTIPROLIFERATIVE EVALUATION

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Cancer remains one of the leading causes of death globally, with an annual increase of about 20 million cases and a mortality rate of 9.6, according to statistics from the World Health Organization (WHO) [1]. Traditional cancer treatments continue to represent the main therapeutic strategies in oncology. Chemotherapy is widely used for its systemic efficacy in suppressing tumor growth and promoting the elimination of malignant cells. However, its use is often complicated by significant limitations, including the development of drug resistance and various adverse effects.

Natural compounds have shown significant potential to induce anti-tumor effects and have historically played a key role in the development of chemotherapeutic agents [2]. Curcumin, a natural polyphenolic compound extracted from the rhizome of *Curcuma longa*, has received considerable interest for its strong anticancer effects. It is involved in several molecular pathways as: the inhibition of cell proliferation, induction of apoptosis, suppression of angiogenesis and modulation of multiple cells signaling pathways involved in cancer progression [3]. The therapeutic potential of curcumin is significantly constrained by its limited bioavailability, mainly due to the instability of its α,β -unsaturated β -diketone core, poor aqueous solubility, extensive metabolism, and rapid systemic elimination. These limitations have prompted the development of structurally related analogues with improved pharmacological properties.

In this context, to overcome these limitations, several chalcone derivatives have been designed and synthesized as curcumin analogues, aiming to improve the chemical stability and preserving or enhancing anticancer activity. A focused structure-activity relationship analysis was performed by introducing halogen substituents at different positions of ring B. These modifications were designed to evaluate the contribution of electronic and positional effects to the antiproliferative activity of the synthesized chalcones.

All the synthesized chalcones were tested against five different cell lines i.e.: follicular thyroid cancer (FTC-133), thyroid carcinoma (8305C), glioblastoma (U87), hepatocellular carcinoma (HEPG2) and osteosarcoma (U2OS), performing an MTT cell proliferation assay. The obtained results of this investigation will be presented and discussed (Figure 1).

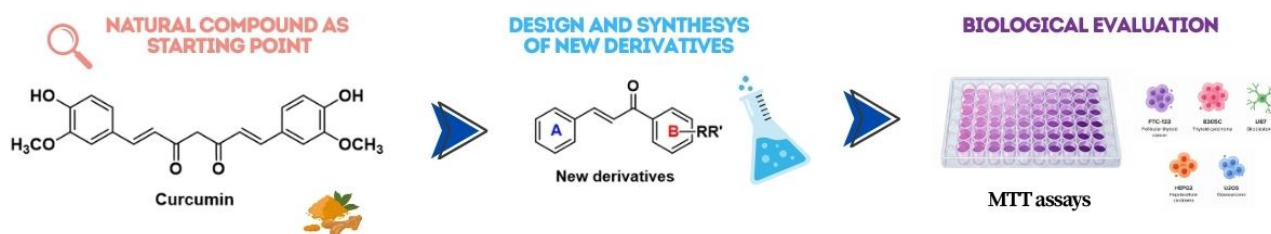


Figure 1: Schematic representation of the overall research workflow.

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Acknowledgements: Project SAMOTHRACE - CUP J43C22000310006 – Identification code ECS00000022

P035

ASYMMETRIC CHALCONES AS RHODESAIN INHIBITORS: EXPLORING COMBINATION STRATEGIES WITH CURCUMIN

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Rhodesain is a cysteine protease that plays a key role in the life cycle of *Trypanosoma brucei rhodesiense*, an endemic parasite in sub-Saharan Africa and responsible for Human African Trypanosomiasis (HAT), a disease that can be fatal if not treated promptly [1]. Due to the limitations associated with current pharmacological HAT therapy, such as route of administration, toxicity, emergence of resistance and spectrum of action, the identification of new targets for the development of antitrypanosomal agents is urgently needed. Rhodesain is involved in multiple biological processes essential for parasite survival, including the evasion of the host immune response and the degradation of both intracellularly transported host proteins and parasite-derived proteins [2]. In this context, the trypanosomal protease represents a promising therapeutic target.

Nutraceuticals have attracted increasing attention in medicinal chemistry as valuable sources of bioactive scaffolds, prompting the investigation of natural compounds such as curcumin. Curcumin is a natural polyphenolic compound derived from the rhizome of *Curcuma longa*, it is well known in literature for its multiple pharmacological activities, as antioxidant, anti-inflammatory, anticancer, neuroprotective, antibacterial and antiparasitic activities [3,4]. It has also been demonstrated to act as a non-competitive inhibitor of rhodesain [5], providing a biologically relevant scaffold for future inhibitor development. On this basis, our research group carried out the synthesis of a new series of asymmetric chalcones derived from this core structure. All compounds were tested against recombinant rhodesain using fluorometric assays to evaluate their kinetic parameters (IC_{50} , K_i). Recently, our research group demonstrated the ability of curcumin to synergistically enhance the pharmacological profiles of our previously synthesized inhibitors when used in combination [5]. For this reason, the most active compound of the chalcones series was evaluated in combination with curcumin against rhodesain, using Chou and Talalay method, to establish if the combination has a synergistic, additive or antagonistic effect [6]. The results of this investigation will be presented and discussed (Figure 1).

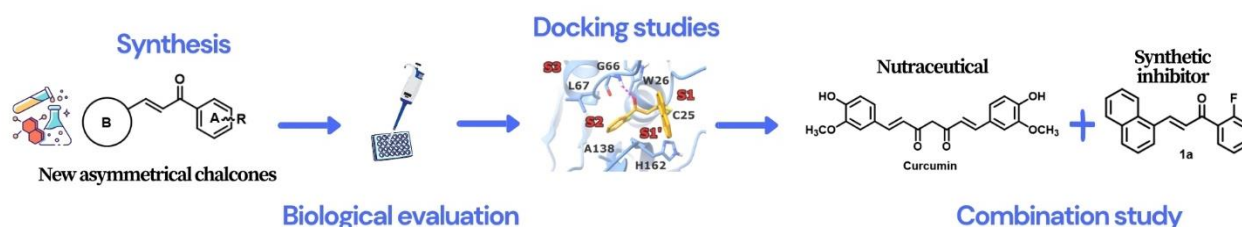


Figure 1: Schematic representation of the overall research workflow.

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P036

**DESIGN, SYNTHESIS, IN VITRO AND IN VIVO LIPIDOMIC PROFILING OF A NOVEL
ADAMANTYLUREIDO-BENZYLAMIDE ANILINE AS FLAP/sEH DUAL INHIBITOR**

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Multitarget approaches represent highly effective strategies for treating both acute and chronic inflammatory diseases [1,2]. In this context, the dual inhibition of FLAP and sEH effectively suppresses pro-inflammatory lipid mediators without compromising pro-resolving pathways and represents a novel underexplored strategy for the treatment of inflammatory conditions [3]. The scarcity of established dual inhibitors represents a significant gap in current medicinal chemistry, and, for this reason we decided to explore the structural requirements needed to modulate these targets. Here, we present the rational design and the synthesis of the adamantylureido-benzylamide aniline compounds, which feature in vitro FLAP/sEH inhibitory activity. Among the synthesized compounds, derivative named LO104 showed the best pharmacological profile and was further analyzed in vivo in a zymosan-induced peritonitis model in mice. Lipidomic profiling of LO104 following in vivo administration highlighted the reduction of 5-LOX/FLAP- and sEH-derived LMs, resulting in a favorable redistribution of LMs in agreement with the inhibition of its molecular targets.

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P037

BIPHENYLAMIDE-BASED DUAL SOCE/DHODH INHIBITORS FOR DIFFICULT-TO-TREAT RHEUMATOID ARTHRITIS: HIT-TO-LEAD OPTIMIZATION AND EX VIVO VALIDATION IN PATIENT-DERIVED PBMCs

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Despite major therapeutic advances, a subset of patients with rheumatoid arthritis (RA) remains refractory to current treatments. "Difficult-to-treat" RA (D2T-RA) defines this high-unmet-need condition, characterized by persistent active or progressive disease despite the failure of multiple biological or targeted synthetic disease-modifying antirheumatic drugs, and by challenging disease management. [1,2] D2T-RA may reflect patient-specific inflammatory mechanisms that contribute to resistance to conventional therapies. Store-operated Ca^{2+} entry (SOCE), mediated by the STIM1/ORAI1 axis, controls Ca^{2+} -calcineurin-NFAT signaling, T-cell activation, effector functions, and cytokine production. [3,4] In this context, genetic associations involving ORAI1, together with ORAI1 variants identified in refractory D2T-RA patients, suggest that altered SOCE may contribute to treatment resistance. [5,6] Beyond SOCE, dihydroorotate dehydrogenase (DHODH) offers a complementary target by sustaining *de novo* pyrimidine biosynthesis and clonal expansion of activated lymphocytes. [7]

Based on this rationale, the identification of a biphenylamide-based hit as a balanced dual SOCE/hDHODH inhibitor, despite a suboptimal safety profile, prompted a pharmacophore-guided SAR exploration of the biphenylamide scaffold. [8,9] This effort led to the identification of a lead compound, showing low-micromolar inhibition of both targets, together with evidence of hDHODH engagement in Jurkat cells. To rationalize hDHODH binding and further support the dual-target pharmacophore model, X-ray crystallography was integrated with molecular modeling and molecular dynamics simulations. The lead compound showed a more favorable cell-viability profile than the single-target SOCE and hDHODH inhibitors Synta66 and teriflunomide, respectively, in both Jurkat cells and peripheral blood mononuclear cells (PBMCs) from healthy volunteers (HVs). Furthermore, it was more effective than Synta66 in reducing TNF- α release in inflamed PBMCs and displayed an excellent *in vitro* metabolic stability. Notably, in PBMCs from two D2T-RA patients carrying ORAI1 variants, p.Pro233Leu and p.Pro51fs, [6] the lead compound reduced SOCE overactivation to levels comparable to those observed in HVs. In the same model, it significantly decreased the expression of selected RA-relevant pro-inflammatory mediators, including TNF, IL-1 β , and IFN γ . Collectively, these data support biphenylamide-based dual SOCE/hDHODH inhibition as a mechanistically grounded and translationally relevant strategy to tackle activation- and proliferation-driven immune dysfunction in D2T-RA.

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P038

DESIGN, SYNTHESIS, AND FUNCTIONAL ASSESSMENT OF OXAZOLOPYRIMIDINES AS MULTITARGET ABC TRANSPORTER INHIBITORS

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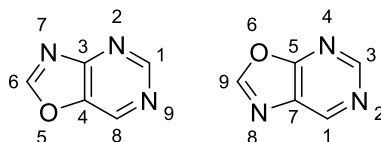
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Over 60% of the ATP-binding cassette (ABC) transporter proteome is undruggable, *i.e.*, many members of this superfamily cannot be targeted by small-molecular drugs despite their involvement in both prevalent and rare human diseases.¹ Target undruggability is a general and major issue in medical life sciences as suitable drug discovery strategies are lacking.² However, structural commonalities between ABC transporters have been suggested which mediate between both polyspecific (*e.g.*, multidrug transporters) and highly specific members for which only few – if any – intrinsic substrates are known.³ The discovery of small-molecules which address these ‘conserved’ binding motifs, and their subsequent optimization to highly specific modulators of undruggable ABC transporters, is the focus of current research.



Recently, we discovered new ABCG2 inhibitors through a computational approach⁴ from which we were able to predict novel template molecules. Amongst those, the oxazolo[4,5-*d*]pyrimidine derivative **1** showed broad activity against the multidrug transporters ABCB1, ABCC1, and ABCG2 already at moderate single-digit to low double-digit micromolar concentrations. Inverting the oxazole moiety (*i.e.* oxazolo[5,4-*d*]pyrimidine **2**) resulted in comparable activity values, and given its better synthetic accessibility, this moiety was chosen for subsequent structure-activity relationship studies.

Aromatic rings at the ethylene piperazinyl linker at position 8/1 were tolerated only if an electron donor was present; otherwise a complete loss of activity was observed. Interestingly, the linker itself without aromatic end also showed broad multitarget activity. An aromatic residue at position 6/9 was crucial for multitarget activity, which could be boosted with *p*-fluoro substitution. Compounds lacking this structural element or showing *o*- or *m*-fluoro substitutions only showed also no activity. While fluoro-phenyl substitutions at positions 1/3 were less tolerated, *p*-bromophenyl boosted multitarget activity. In essence, we identified crucial structural elements at three positions of the oxazolo[4,5-*d*]pyrimidine moiety that triggered multitarget activity against ABCB1, ABCC1, and ABCG2. Derivatives synthesized harboring these structural elements do not only represent valuable anchors in the exploration of the ‘dark’ ABC transporter proteome, but also new templates for therapeutic intervention against multidrug transporters-mediated diseases, *e.g.*, multidrug resistance.

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P039

IN-DEPTH INVESTIGATION OF THE FIRST CB2R-TARGETED ALLOSTERIC MODULATOR: FROM METABOLOMICS AND PROTEOMICS TO RADIOTRACER DEVELOPMENT FOR TUMOR IMAGING

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The interplay between cancer biology and cannabinoid receptor type 2 (CB2R) has been extensively studied, yet many uncertainties remain, driving increased research efforts with molecular imaging tools. In this context, Positron Emission Tomography (PET), a molecular imaging modality distinguished by its high sensitivity for the early and quantitative assessment of cancer-related biological processes, recognizes the value of CB2R as a promising imaging biomarker, particularly in light of its elevated expression in several tumors [1,2]. CB2R-targeted PET radioligand development has so far remained confined to preclinical investigation due to major drawbacks, including high nonspecific binding, metabolic instability, poor pharmacokinetics, and insufficient subtype selectivity over the closely related cannabinoid receptor type 1 (CB1R), whose widespread expression may generate off-target PET signals [3].

This study aims to develop the first allosteric CB2R radiotracer for tumor imaging, exploiting the superior receptor subtype selectivity achievable through allosteric modulation compared with conventional orthosteric ligands. The study is centered on EC21a, the first reported small-molecule CB2R PAM, characterized by nanomolar CB2R affinity and high selectivity over CB1R [4,5].

The project integrates preliminary pharmacokinetic, metabolomic, and proteomic investigations on the native ligand to better elucidate EC21a's mechanism of action and potential off-target effects. This knowledge will guide the synthesis and preclinical evaluation of the radiolabeled analogue [¹⁸F]EC21a, which will undergo *in vitro* uptake studies in healthy and promyelocytic leukemia HL-60 cells—selected for their CB2R expression and diagnostic relevance—prior to *in vivo* PET imaging investigations.

Overall, the project aims to establish an innovative allosteric radiotracer platform capable of improving CB2R-targeted tumor imaging specificity and advancing the translational potential of CB2R PET radiopharmaceuticals.

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P040

5-HTR_{1A} ANTAGONIST FOR TARGETING IN PROSTATE CANCER CELLS

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Prostate cancer (PCa) is one of the most prevalent malignancies affecting men worldwide. Increasing evidence indicates that serotonin (5-hydroxytryptamine, 5-HT) also plays a significant role in cancer biology. In particular, serotonin has been implicated in promoting oncogenic processes through its trophic, mitogenic, and anti-apoptotic effects, including in prostate cancer. Many of these biological effects are primarily mediated by the 5-HT subtype 1A receptor (5-HTR_{1A}). In this context, we investigated a series of synthesized serotonergic ligands characterized by high affinity and selectivity for 5-HTR_{1A}, with the aim of evaluating their ability to modulate serotonin-driven signaling pathways in several prostate cancer cell lines, including PC3, DU145, and LNCaP. Among the tested compounds, we selected a promising ligand (3g) for further investigation, as it acts as a 5-HTR_{1A} receptor antagonist. Compound 3g was able to inhibit serotonin-mediated signaling by reducing ERK phosphorylation, a key pathway involved in cell proliferation and survival. This effect was particularly evident in androgen-independent DU145 cells, in which treatment with 3g induced apoptosis. Importantly, this pro-apoptotic activity appeared to be selective for cancer cells, as no adverse effects on the viability of benign prostate epithelial cells were observed. Beyond its impact on cell survival, 3g also influenced the stem-like characteristics of DU145 cells, and in androgen-sensitive LNCaP cells, the compound was found to maintain androgen receptor (AR) expression. In addition, compound 3g was subjected to molecular docking studies and, as a result, the conformational rigidity conferred by its core scaffold and the appropriately positioned piperazine moiety makes this ligand capable of properly interacting with key amino acid residues of the 5-HTR_{1A} receptor (Figure 1). Taking together, these results highlight the ability of the 5-HTR_{1A} ligand 3g to modulate serotonin-driven oncogenic pathways in both androgen-dependent and androgen-independent prostate cancer models. By simultaneously affecting cell proliferation, apoptosis, stem-like properties, and androgen receptor expression, 3g emerges as a promising candidate for further investigation and development as a novel therapeutic agent for prostate cancer.

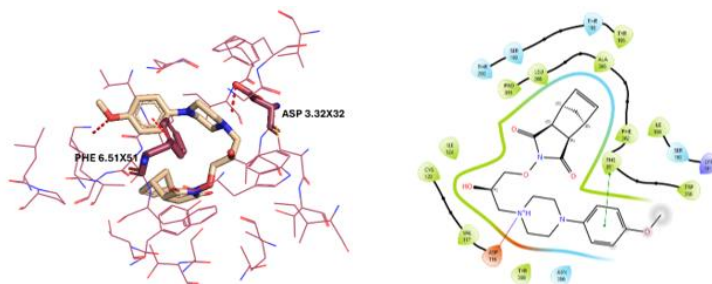


Figure 1. 2D and 3D representation of synthesized 3g compound in complex with 5-HT_{1A} receptor.

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P041

IDENTIFICATION OF NATURAL HDAC8 INHIBITORS THROUGH SHAPE VIRTUAL SCREENING AND *IN VITRO* VALIDATION: UNVEILING THE APOPTOTIC ANTICANCER MECHANISM

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Histone deacetylase 8 (HDAC8) is a key epigenetic regulator often overexpressed in various human malignancies, making it a promising therapeutic target. Since current clinically approved HDAC inhibitors face limitations due to poor selectivity and off-target toxicity, discovering novel and diverse scaffolds from natural sources is of primary interest [1].

In this study, a shape-based virtual screening was performed on a dataset of 307,814 natural compounds from the ZINC database, using the bioactive conformations of five co-crystallized HDAC8 ligands as templates. Promising hits were selected via molecular docking, MM-GBSA binding free energy evaluation, both performed on the PDB model 5FCW [2], and fingerprint-based clustering analysis. The enzymatic inhibition of the top hits was validated *in vitro* using fluorometric assays. The antiproliferative profile and cellular mechanism of action were extensively evaluated across human cancer cell lines through MTT, clonogenic assays, continuous live-cell imaging, Annexin V staining, and ROS intracellular measurement. Finally, a 1 μ s molecular dynamics (MD) simulation was carried out to assess target-ligand stability (Fig. 1). Computational screening successfully prioritized 40 natural molecules. Among them, Compound 2 emerged as the most potent hit, exhibiting more than 97% inhibition at 1 μ M concentration and dose-dependent cytotoxicity. Time-lapse microscopy and Annexin V staining revealed that Compound 2 rapidly triggers apoptotic cell death, marked by cell shrinkage and membrane blebbing, alongside mitotic impairment. Furthermore, a significant increase in intracellular ROS levels and early nuclear area expansion were observed, consistent with target hyperacetylation. Long-term MD simulations confirmed that Compound 2 forms a highly stable interaction network within the HDAC8 active site, optimally coordinating the catalytic Zn²⁺ ion. Our findings demonstrate that Compound 2 is a novel, naturally derived HDAC8 inhibitor capable of inducing apoptosis and mitotic arrest in solid tumor cells, highlighting its potential for further hit-to-lead optimisation.

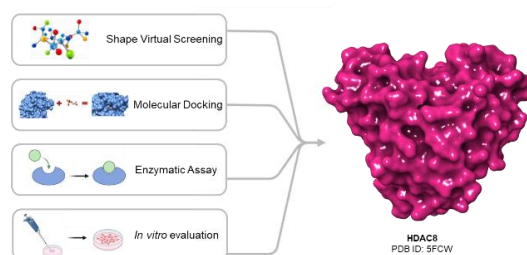


Figure 1. Computational and experimental pipeline for HDAC8 drug discovery.

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P042

NEW ANTICANCER AGENTS FROM A BERBERINE-BASED STRUCTURAL SIMPLIFICATION
APPROACH

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Natural products represent an invaluable source of bioactive scaffolds for the rational design and development of novel therapeutic agents [1-3]. In this study, berberine (BBR), an isoquinoline alkaloid isolated from medicinal plants (e.g. *Berberis Aristata*, *Coptis Chinensi*, *Hydrastis Canadensis*), and widely recognized for its anticancer properties [4-5], was selected as the starting point for the generation of a focused library of BBR-simplified derivatives. To investigate their potential antitumoral profile, the Inverse Virtual Screening target fishing approach was employed [6], considering a comprehensive panel of cancer-related protein targets containing 6688 entries. Computational analyses suggested that several compounds may effectively interact with multiple validated targets involved in tumor progression and survival pathways. Notably, a favorable predicted binding affinity (threshold=-6.2 kcal/mol) was observed for albumin (ALBU_HUMAN), protein arginine N-methyltransferase 5 (ANM5_HUMAN), bromodomain-containing protein 2 (BRD2_HUMAN), bromodomain-containing protein 4 (BRD4_HUMAN), dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYR1A_HUMAN), dual specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2_HUMAN), epidermal growth factor receptor (EGFR_HUMAN), estrogen receptor (ESR1_HUMAN), glutathione S-transferase omega-1 (GSTO1_HUMAN), isocitrate dehydrogenase [NADP] cytoplasmic (IDHC_HUMAN), methylosome protein WDR77 (MEP50_HUMAN), ribosyldihydronicotinamide dehydrogenase (NQO2_HUMAN), histone-lysine N-methyltransferase NSD2 (NSD2_HUMAN), phosphatidylinositol 5-phosphate 4-kinase type-2 alpha (PI42A_HUMAN), dual specificity protein kinase TTK (TTK_HUMAN). To further validate these findings and assess the biological potential of the most promising derivatives, both in vitro binding affinity assays and cell-based assays on selected human cancer cell lines are currently in progress.

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P043

MECHANISTIC INVESTIGATION AND TARGET VALIDATION OF BITHIAZOLE DERIVATIVES AS
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Thiazole-based small molecules play a privileged role in medicinal chemistry: several compounds in this class have been reported to exhibit antibacterial, antifungal, and antiproliferative effects, and more than 15 FDA-approved compounds are present [1]. Furthermore, the extension of the thiazole moiety led to the identification of bithiazoles, which have recently gained even greater interest in medicinal chemistry, as they have been shown to recover misfolded cystic fibrosis transmembrane regulator (CFTR) and α -sarcoglycan, which are implicated in cystic fibrosis and sarcoglycanopathies, respectively [2]. In particular, 4'-Methyl-4,5'-bithiazoles has been used as correctors of folding-defective CFTR mutants. In this context, a study based on structure-activity relationships (SAR) stemming from compounds **C17**, originally developed as a CFTR corrector, led to the identification of **C17**-derivatives, which were tested in myogenic cells, revealing their ability to recover α -sarcoglycan misfolding both *in vitro* and *in vivo*, thus expanding putative candidates for treating sarcoglycanopathies [3]. Although **C17** and its derivatives have promising potential in the field of misfolded protein diseases, the molecular mechanisms underlying their biological effects remain poorly elucidated since unknown interactors are involved in the pathogenic pathway. So, for this reason, the search for the macromolecular interactors of bithiazoles is wide open, and we report the synthesis and characterization of a small set of **C17**-derivatives, comprising several compounds, including **C17** fragments, to evaluate which of these are involved in α -sarcoglycan recruitment in myogenic cells [4]. α -sarcoglycan interactors are being identified by affinity chromatography using beads functionalized with **C17**-derivatives. To rationalize the results and validate the targets, protein-protein molecular docking is being performed.

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P044

TARGETED DEGRADATION OF THE ZEB1-ALDH1A3 AXIS IN CANCER USING PROTACS AND OLIGONUCLEOTIDE-BASED PROTACS

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"Undruggable" proteins play significant roles in various diseases but are hard or impossible to target with conventional drugs, thus representing a major setback in drug discovery. Zinc-finger E-box binding homeobox 1 (ZEB1) is a significant example of such a "hard-to-drug" challenge as it lacks a suitable ligand-binding pocket, and little is known about its structure. ZEB1 is a transcription factor that drives cancer cell invasiveness by promoting the epithelial-to-mesenchymal transition¹. In addition, neutrophils expanding in the tumor microenvironment overexpress this transcription factor which, when complexed with neutrophil extracellular traps, induces immunosuppression, thereby contributing to relapses and metastasis.

Hence, ZEB1 emerges as a key target for cancer therapy. To overcome its undruggability, we applied diverse targeted protein degradation strategies towards both its **direct** and **indirect** modulation.

i) Direct approach. Inspired by the successful platform described in the literature², we designed oligodeoxynucleotide decoys (ODNs) capable of binding to ZEB1 two zinc finger domains. After validating target engagement, we used azide-bearing ODNs as warheads for oligonucleotide-based proteolysis targeting chimeras (oligo-PROTACs), assembled *via* a copper-free strain-promoted azide-alkyne cycloaddition (SPAAC) reaction.

ii) Indirect approach. In tumors, ZEB1 expression is influenced by aldehyde dehydrogenase 1A3 (ALDH1A3), an enzyme that fosters proliferation of cancer stem cells - a tumor subpopulation endowed with drug resistance, high metastatic potential and self-renewal³. Moreover, through the suppression of microRNA-200, it positively modulates the expression of ZEB1, contributing to increased invasiveness of cancer cells. It follows that targeting the whole ZEB1-ALDH1A3 axis represents a potential pharmacological strategy to counteract tumor growth and stemness of cancer stem cells. Therefore, building on two previously reported ALDH1A3 selective inhibitors^{4,5}, we designed and synthesized PROTACs to induce the chemical knockdown of this enzyme, thereby inhibiting its role in cancer progression and indirectly downregulating ZEB1.

Overall, by leveraging direct and indirect strategies, we present the first-in-class tools to address ZEB1 hard-to-drug nature, providing a framework for the modulation of other challenging transcription factors. Besides this, our strategy holds promise for disrupting critical cancer-related pathways involved in tumor progression and metastasis.

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P045

IN SILICO EVALUATION OF BIOACTIVE CONSTITUENTS FROM A FUNCTIONAL BEVERAGE TARGETING HUMAN PANCREATIC LIPASE

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Human Pancreatic Lipase is the main enzyme responsible for the hydrolysis and absorption of dietary lipids and represents a relevant target for nutritional strategies aimed at weight management^[1]. Virtual screening approaches^[2] can support the identification of bioactive compounds with potential Lipase inhibitory activity. This study aimed to evaluate the binding potential of bioactive compounds associated with the ingredients of a functional beverage toward Human Pancreatic Lipase through molecular docking analysis. Compounds were selected based on the qualitative composition of the functional beverage and screened against Human Pancreatic Lipase using the Glide^[3] molecular docking software (Schrödinger). Binding poses were evaluated according to Glide Score values and the interactions established within the enzyme active site. Compounds were subsequently ranked based on their predicted binding affinity. The virtual screening identified several compounds exhibiting favorable binding profiles toward Human Pancreatic Lipase. The top-ranked ligands showed strong predicted affinity and established interactions with key residues involved in substrate recognition and catalytic activity. These findings suggest that specific bioactive constituents of the beverage may contribute to the modulation of lipid digestion. Molecular docking analysis highlighted a subset of compounds with promising binding characteristics toward Human Pancreatic Lipase. These results provide a rational basis for further experimental investigations to validate their inhibitory potential and clarify their possible contribution to the biological activity associated with the functional beverage.

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P046

SYNTHESIS AND BIOLOGICAL EVALUATION OF UROLITHIN A DERIVATIVES

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Urolithin A (Uro A) is a natural bioactive compound belonging to the class of urolithins, which are dibenzo[*b,d*]pyran-6-one derivatives characterized by benzo-coumarin scaffolds with varying hydroxylation patterns, synthesized by gut microbiota following the ingestion of foods rich in ellagic acid and ellagitannins [1, 2]. Despite its several biological properties, Uro A exhibits a poor bioavailability and its biosynthesis varies among individuals depending on different factors, as the composition and functionality of the gut microbiota, sex, age, health, lifestyle, diet and polyphenols consumption [3,4]. Literature data reported the synthesis of some Uro A derivatives, which possess a benzo[*c*]chromen-6-one scaffold in common, exploiting different synthetic methodologies [5,6]. However, one of the simplest strategies employs starting materials with electron-donating groups, like phloroglucinol and resorcinol. That being considered, the main goals of this work are the synthesis and biological evaluation of some Uro A derivatives (Fig. 1). The synthetic procedures showed good selectivity and reproducibility, obtaining the desired compounds in good yields. All the compounds have been fully characterized and evaluated for their anticancer, antioxidant and anti-inflammatory activities, by the means of *in vitro* and cell-based assays. The obtained results will give new hints about the potential therapeutic use of Uro A derivatives, overcoming the already known limitations.

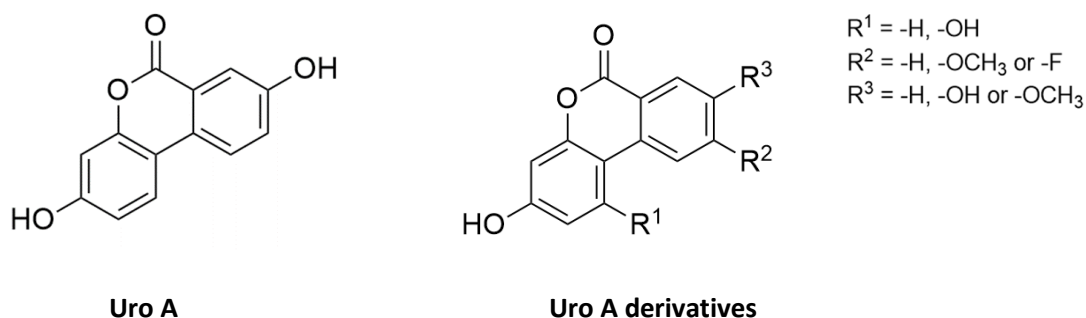


Figure 1. Structures of Uro A and its synthesized derivatives.

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P047

FIRST-IN-CLASS X-RAY-ACTIVATABLE PARPi PRODRUGS FOR SPATIOTEMPORAL CONTROL OF PARP1 INHIBITION IN SOLID TUMORS: DESIGN AND IN SILICO EVALUATION

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Poly(ADP-ribose) polymerase inhibitors (PARPi) are highly effective agents that induce synthetic lethality in homologous recombination-deficient tumors, including triple-negative breast, ovarian, and endometrial cancers. However, their limited selectivity results in significant systemic toxicities, restricting their clinical applicability [1]. In the context of anticancer therapy, a growing frontier in medicinal chemistry is represented by the development of advanced prodrug systems designed as externally activatable therapeutic tools. In this regard, different external stimuli are currently being investigated, including light, ionizing radiation, and ultrasound [2]. Among these, X-ray-responsive systems are particularly attractive due to their deep tissue penetration and their established clinical use in radiotherapy (RT), enabling localized drug activation within irradiated tumor tissues and synergistic therapeutic effects [2–4]. PARPi are currently used in combination with RT in established therapeutic protocols, where ionizing radiation enhances DNA damage and potentiates PARP inhibition. This therapeutic interplay provides the rationale for the development of X-ray-activatable PARPi prodrugs.

Herein, we report the rational design of the first X-ray-activatable prodrugs of clinically approved PARP inhibitors (Figure 1). In details, a comprehensive analysis of available PARP1-ligand crystallographic structures was carried out to identify key and recurrent binding interactions and to define suitable positions for chemical modification. On this basis, a focused library of putative prodrugs was generated by selectively masking critical interaction motifs to enforce an inactive OFF-state. Different classes of radiation-responsive caging groups were introduced, including azides, N-oxides, N-alkylpicolinium, dihydroxybenzyl, azo linkers, and metal-based cages, all known to undergo cleavage upon exposure to ionizing radiation. The impact of these modifications on PARP1 binding was systematically evaluated through in silico studies, assessing the extent to which target engagement is suppressed prior to activation, together with the prediction of key ADMET properties.

X-ray-responsive prodrugs: controlled, on-demand activation

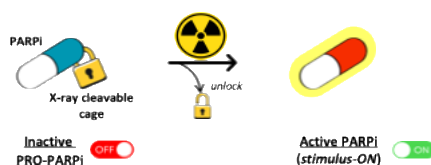


Figure 1. Rationale for the design of X-ray-cleavable PARP inhibitor prodrugs.

Overall, these results provide a starting point for a first-in-class strategy based on X-ray-activatable PARP inhibitor prodrugs, enabling site-selective drug activation while leveraging the synergy between PARP inhibition and radiotherapy. The most promising candidates identified herein will be synthesized and experimentally evaluated in subsequent studies.

Acknowledgments: Gabriele La Monica was supported by a AIRC fellowship for Italy (Italy Post-Doc ID 33270-2025) under the supervision of Prof. Annamaria Martorana.

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P048

UNLOCKING THE *UNDRUGGABLE*: COMPUTER-AIDED STRATEGIES FOR TARGETING RHOA

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The protein RHOA is a key regulator of physiological processes in healthy cells [1,2]; however, it also plays a significant role in cancer progression, exerting its effects through interactions with downstream effectors such as ROCK1 [3,4]. Indeed, the signaling axis mediated by the RHOA/ROCK1 interaction is increasingly recognized as a critical driver of metastatic behavior and tumor cell invasiveness across multiple cancer types [5–10]. However, targeting the RHOA/ROCK1 protein–protein interaction remains a promising yet challenging strategy for inhibiting oncogenic signaling [11]. RHOA is widely considered *undruggable* due to the absence of well-defined binding pockets [12]. However, recent studies indicate that conformation-specific dynamic pockets can enable new therapeutic opportunities for drug discovery [13]. Here, we combine large-scale structural analyses, molecular dynamics simulations, and alchemical free energy calculations to uncover and characterize a dynamic, druggable site at the RHOA/ROCK1 interface. We performed extensive alchemical free energy calculations on a set of mutations spanning the interface. Our results identify a network of key residues that critically stabilize the RHOA/ROCK1 interaction. Building on these findings, we conducted structure-based virtual screening targeting a newly identified pocket defined by these residues and also identified small molecules capable of binding to it. These molecules represent an optimal starting point towards inhibitors of the RHOA/ROCK1 interaction.

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P049

TARGETING MAGL THROUGH REVERSIBLE INHIBITION: EXPANSION OF A PIPERIDINE-BASED CHEMICAL SPACE

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Monoacylglycerol lipase (MAGL) is a key serine hydrolase responsible for the hydrolysis of 2-arachidonoylglycerol (2-AG), thus regulating endocannabinoid signaling and contributing to several pathological conditions, including inflammation, pain, and neurodegeneration [1]. Moreover, MAGL catalyzes the hydrolysis of monoacylglycerols into glycerol and free fatty acids, thus producing lipid signaling molecules that promote tumorigenesis and metastasis and supplying metabolic substrates that support tumor growth. Inhibition of MAGL leads to increased 2-AG levels and a consequent reduced production of arachidonic acid-derived mediators, resulting in anti-inflammatory effect [1]. Despite the therapeutic potential of this approach, most of the MAGL inhibitors reported to date act through irreversible mechanisms, often associated with adverse effects upon chronic treatment [2]. In this context, we focused on the development of reversible MAGL inhibitors based on a benzyl/phenyl-piperidine scaffold previously identified by our group as a MAGL reversible inhibitor ($IC_{50} = 24.3 \mu M$) (**A**, Figure 1) [3]. Structure-based computational studies provided insights into the binding mode of the lead compound within the enzyme active site, highlighting the presence of a polar region accommodating the glycerol moiety of 2-AG and a large hydrophobic channel, hosting the long unsaturated chain of 2-AG [3]. Guided by these findings, a focused library of structurally diverse derivatives (**B**, Figure 1) was rationally designed and synthesized through targeted modifications on both sides of the scaffold. In particular, phenol bioisosteres were introduced to modulate key interactions within the polar region, while lipophilic substituents and bioisosteric replacement of the distal phenyl ring were explored to optimize interactions within the hydrophobic channel. All synthesized derivatives were systematically evaluated in enzymatic assays on human MAGL. Several compounds exhibited a marked improvement in inhibitory activity compared to the starting scaffold, achieving up to a 100-fold increase in potency. Pre-incubation experiments confirmed a fully reversible mechanism of inhibition. These findings support the potential of the piperidine-based scaffold as a robust starting point for the development of reversible MAGL inhibitors and provide a framework for further optimization toward therapeutically relevant candidates.

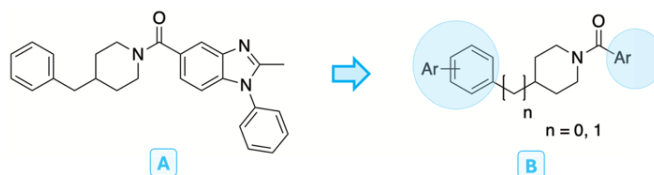


Figure 1. Structure of starting benzylpiperidine (**A**) and general scaffold of the newly synthesized derivatives (**B**).

References:

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P050

DESIGN OF NEW REVERSIBLE MAGL INHIBITORS VIA BIOISOSTERIC REPLACEMENT OF THE PIPERAZINE CORE

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Monoacylglycerol lipase (MAGL) is a key enzyme of the endocannabinoid system (ECS), which regulates a wide range of physiological processes. The ECS is also implicated in pathological conditions such as pain, inflammation and neurodegenerative diseases. MAGL is the main enzyme responsible for the hydrolysis of 2-arachidonoylglycerol (2-AG), the most abundant endocannabinoid in the human body, and it also links the ECS to lipid metabolism as it is responsible for the hydrolysis of monoacylglycerols. Notably, MAGL is often overexpressed in aggressive cancer cells, driving the production of oncogenic lipids that promote invasion, migration and tumor growth. Thus, MAGL inhibition represents a promising anticancer strategy. However, most reported inhibitors act through an irreversible mechanism, leading to adverse effects in animal models [1], while few reversible and selective inhibitors are available, leaving this a relatively underexplored area of research.

Based on the previously published compound **1** (Figure 1) [2], a potent and reversible MAGL inhibitor ($IC_{50} = 5.2$ nM), we designed and synthesized new derivatives by replacing the central piperazine core with bioisosteric moieties to investigate the impact of this modification on inhibitory activity, with the aim of identifying more potent derivatives.

The inhibitory activity of the compounds on hMAGL was assessed through spectrophotometric enzymatic assays using 4-nitrophenylacetate as the substrate. The most promising compounds were further investigated by co-crystallization studies with recombinant MAGL produced in *E. Coli* and purified, to elucidate their binding mode and key interactions.

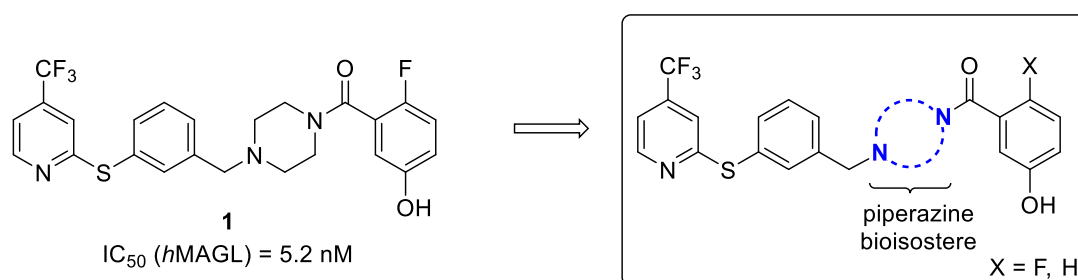


Figure 1. Schematic representation of the newly designed MAGL inhibitors.

References:

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P051

SYNTHESIS AND PRELIMINARY EVALUATION OF AKR INHIBITORS AS PROSPECTIVE AGENTS FOR THE MANAGEMENT OF CANCER AND DIABETES MELLITUS COMPLICATIONS

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Human aldo-keto reductases (AKRs) are a superfamily of NADPH-dependent enzymes that reduce endogenous and exogenous carbonyl compounds to their corresponding alcohols. Beyond their roles in cellular homeostasis—including detoxification of reactive lipid-derived aldehydes, isoprenoid, and retinal metabolism—dysregulation of specific AKR isoforms has emerged as a key factor in the pathogenesis of major human diseases, notably cancer and diabetes mellitus (DM), making these enzymes attractive therapeutic targets.

Among AKRs, AKR1B1 (aldose reductase) is the most extensively characterized isoform due to its pivotal role in glucose metabolism and diabetic complications. It catalyzes the rate-limiting step of the polyol pathway, which is largely inactive under physiological conditions but becomes markedly upregulated in hyperglycaemic states such as DM, leading to oxidative stress, inflammation, and tissue damage that drive the development of chronic diabetic complications, including neuropathy, nephropathy, and retinopathy. In cancer, the pro-oxidative tumor microenvironment induces the overexpression of several AKRs, particularly AKR1B1 and AKR1B10, thereby promoting tumor progression through metabolic reprogramming and detoxification of reactive aldehydes. AKR1B1 has also been linked to epithelial–mesenchymal transition, connecting it to cancer dissemination and fibrosis. Moreover, prolonged exposure to anticancer agents (*e.g.* anthracyclines, platinum compounds, cyclophosphamide, methotrexate, vinca alkaloids) upregulates multiple AKR isoforms (AKR1B1, AKR1B10, AKR1C1, AKR1C3), contributing to chemoresistance.

Collectively, these findings highlight AKRs as key mediators of metabolic dysregulation, oxidative stress, and drug resistance, underscoring the need for effective AKR inhibitors. In this context, we recently identified (5-arylidene-4-oxothiazolidin-3-yl)alkanoic acids as potent AKR1B1 inhibitors capable of modulating the polyol pathway in human lens epithelial and retinal glial cells [1,2]. Additionally, benzoic acid-based analogues showed selective activity against AKR1B10 and AKR1C3 and enhanced daunorubicin cytotoxicity in A549 cells [3]. Here, we report the design, synthesis, and biological evaluation of new derivatives to investigate the effect of substituents at positions 3 and 5 of the thiazolidinone scaffold on potency and selectivity. In parallel, structurally distinct benzoic acid-based carboxamides were developed and assessed as novel AKR inhibitors.

References:

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P052

RATIONAL DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF *N*-[(3,5-DIMETHYLPHENYL)METHYL]-1*H*-BENZIMIDAZOLE DERIVATIVES AS PORCINE PANCREATIC ELASTASE INHIBITORS

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Human skin elasticity and structural stability depend on extracellular matrix proteins, particularly collagen and elastin. Elastase 1, a serine protease expressed in keratinocytes, contributes to elastin proteolysis, and its overactivity has been associated with skin aging and disorders such as psoriasis and dermatitis [1]. Therefore, selective elastase inhibitors are promising candidates for dermatological and cosmetic applications. Recently, a small series of *N*-[(3,5-dimethylphenyl)methyl]-1*H*-benzimidazole derivatives was identified as inhibitors of porcine pancreatic elastase (PPE), a widely used surrogate model for preliminary biochemical evaluation [2,3]. Guided by computational modeling insights, we designed a novel series of *N*-[(3,5-dimethylphenyl)methyl]-1*H*-benzimidazole derivatives (Figure 1), with the aim of enhancing inhibitory activity. To improve the synthetic efficiency and sustainability we applied new synthetic routes by applying greener solvents.

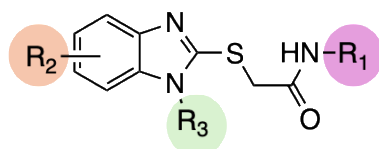


Figure 1. Representative scaffold of the designed benzimidazole-based derivatives with variable substitution sites.

In detail, to gain further structure–activity relationship (SAR) insights against PPE inhibition, a systematic structural modification was introduced on the *N*-phenylacetamide moiety (R_1) as well as on the benzimidazole scaffold (R_2) and explored the *N*-1 side chain (R_3) by introducing distinct alkyl/aryl substituents. Notably, several compounds exhibited significant anti-elastase activity in the micromolar range, further supporting the potential of this chemical class as a valuable alternative to previously reported chemotypes, which mainly act through irreversible inhibition mechanisms. The biological results also provided additional insights into the structural features governing enzyme recognition and inhibitory potency within this scaffold. Molecular docking studies were consistent with the experimental SAR findings, highlighting the crucial role of hydrophobic contacts and aromatic interactions in stabilizing ligand binding within the PPE active site and, consequently, in modulating inhibitory activity.

References:

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P053

MOLECULAR DYNAMICS-GUIDED STRUCTURE-BASED VIRTUAL SCREENING REVEALS NOVEL CANDIDATE LIGANDS TARGETING THE WEST NILE VIRUS RNA G-QUADRUPLIX

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West Nile virus (WNV) remains a significant global health concern, with limited therapeutic options currently available. Recent structural studies have identified a highly conserved RNA G-quadruplex (G4) within the viral genome, located in the region encoding the methyltransferase domain of the NS5 protein (NS5-B). This RNA secondary structure has been proposed to play a regulatory role in viral replication and gene expression, making it an attractive target for antiviral drug discovery. The recently solved crystal structure of this G4 (PDB ID: 8UTG) has provided the first high-resolution structural framework for investigating its conformational dynamics and druggability [1].

In this perspective, we prepared the WNV G4 structure using the CHARMM-GUI platform and subjected it to an all-atom molecular dynamics (MD) simulation for 1000 ns with the GROMACS package [2]. Trajectory analyses, including root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and conformational matrix analysis, revealed two predominant, recurrent conformational states. These representative conformations, together with the experimental X-ray structure, were subsequently employed for structure-based virtual screening. Particular attention was dedicated to a peculiar binding pocket defined by the A6–A20 adenine dyad and the G6–U15–U19 γ -triad, with the aim of identifying selective ligands capable of recognizing this unique structural feature of the RNA G4.

After confirming the druggability of this binding pocket through SiteMap analysis [3], a rigorous virtual screening workflow integrating multiple force fields and consensus scoring strategies identified seven promising candidate molecules.

These compounds will be further evaluated through biophysical assays to validate their direct interaction with the WNV RNA G4, followed by antiviral assays to assess their ability to inhibit viral replication.

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P054

LIGHT-MODULABLE DUAL AChE/MAO-B INHIBITION VIA AURONE-BASED MOLECULAR PHOTOSWITCHES

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The multifactorial nature of neurodegenerative disorders, such as Alzheimer's Disease (AD), demands innovative therapeutic strategies. Multitarget-Directed Ligands (MTDLs) are currently being investigated for their potential to treat the complex pathology of AD by simultaneously modulating multiple pathways.[1] In this context, we report the development of a new family of aurone-based molecular photoswitches designed for the spatiotemporal control of both acetylcholinesterase (AChE) and monoamine oxidase B (MAO-B) activity, which are two established AD-related drug targets. Building on a previously identified 2-benzylideneindan-1-one lead,[2,3] we employed an isosteric substitution strategy to fine-tune the electronic properties of the chromophore (Figure 1). This modification successfully induced a significant 30 nm bathochromic shift of the isosbestic point, allowing for reversible Z/E photoisomerization within a safer biological window. In vitro enzyme assays confirmed that these aurone derivatives act as potent dual-target inhibitors with sub-micromolar inhibition potency. Notably, the optimization of the amino group led to high isoform selectivity and significant light-modulated inhibitory potency. These findings validate the aurone moiety as a versatile scaffold for high-precision photopharmacology, ultimately providing a promising starting point for the development of light-controlled MTDLs against neurodegeneration.

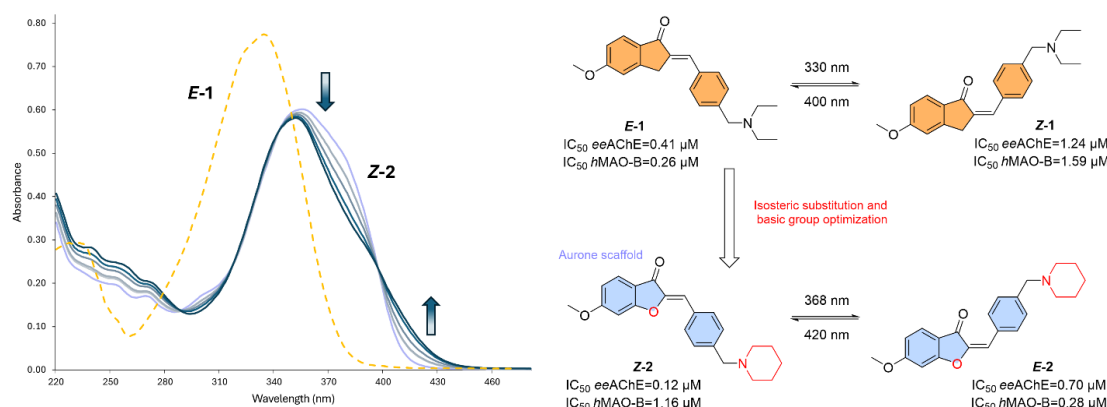


Figure 1: (Left) UV-Vis spectra of aurone **2** showing the Z→E photoisomerization at 368 nm in methanol compared to the lead compound **E-1**. (Right) Structure refinement and light-dependent modulation of dual AChE/MAO-B inhibitory activity.

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P055

DISCOVERY OF A NOVEL WATER-SOLUBLE PRODRUG OF MEDS433: IMPROVING SOLUBILITY AND BIOAVAILABILITY OF A POTENT *h*DHODH INHIBITOR FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

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MEDS433 is a potent inhibitor of *human* dihydroorotate dehydrogenase (*h*DHODH) developed by Drug Discovery and Clinic (DDC) s.r.l, a Spin-off of the University of Torino. It displays nanomolar activity on the isolated enzyme (IC₅₀ = 1.2 nM), strong antiproliferative effects in Acute Myeloid Leukemia (AML) cellular models, and broad antiviral activity. [1,2] Significant *in vivo* efficacy in preclinical AML models, together with a favourable toxicity profile, identified MEDS433 as a promising drug candidate. However, its limited aqueous solubility and oral bioavailability highlighted opportunities for further optimization to improve *in vivo* performance at lower doses.

To address these liabilities, a prodrug approach was applied, leading to the development of a water-soluble prodrug. The obtained prodrug, MEDS758, showed a 600-fold increase in aqueous solubility and was rapidly converted to the parent compound following both oral and intravenous administration in mice. Notably, MEDS758 markedly improved the oral bioavailability of MEDS433, increasing it from 54% to 100% and effectively overcoming solubility-limited absorption (Figure 1).

Overall, MEDS758 represents the first reported prodrug of an *h*DHODH inhibitor, significantly enhancing the drug-like properties of MEDS433 and supporting its progression into early drug development. These advances have enabled the transition of the compound into preclinical development in collaboration with an international CRO, representing a key step toward clinical evaluation in haematological indications.

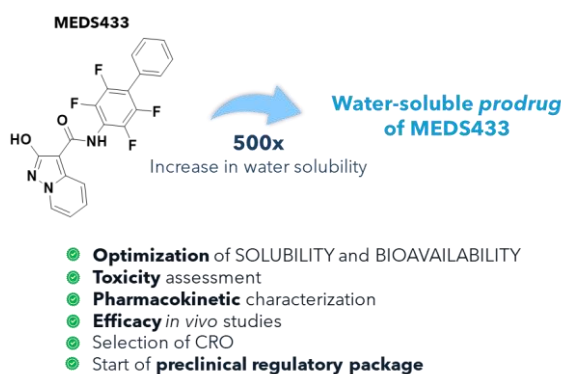


Figure 1. Prodrug optimization of MEDS433 to improve solubility and oral bioavailability.

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P056

ARTIFICIAL INTELLIGENCE-GUIDED REPURPOSING REVEALS A SMOOTHENED- AND SIRT1-DEPENDENT MECHANISM BEHIND THE PROMYELINATING ACTIVITY OF LAQUINIMOD

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Despite the availability of disease-modifying therapies, the development of effective pro-remyelinating strategies remains a major unmet need in multiple sclerosis (MS). Here, we leveraged an artificial intelligence (AI)-guided, target-informed structural similarity screening approach for drug repurposing, using a well-characterised pro-myelinating compound with a defined molecular target as a reference scaffold. This strategy uncovered a previously unrecognised structural similarity between Laquinimod and GSA-10, a pro-myelinating agent that enhances oligodendrocyte progenitor cell (OPC) differentiation into myelinating oligodendrocytes (OLs). Consistent with this, Laquinimod enhances myelin gene expression in human iPSC-derived oligodendrocytes at nanomolar concentrations. Mechanistically, we provide genetic and pharmacological evidence that Laquinimod promotes myelin gene expression by modulating the Smoothened (SMO) receptor and activating AMPK signalling. Importantly, our findings identify SIRT1, a histone deacetylase, as a critical downstream effector of the SMO-AMPK pathway that controls Myelin Basic Protein (MBP) gene expression, thereby revealing a previously unrecognised signalling axis that regulates the differentiation of premyelinating OLs. These findings have significant therapeutic implications, highlighting Laquinimod's potential for remyelination therapy at nanomolar concentrations. More broadly, our study demonstrates the power of AI-guided, target-informed structural repurposing to uncover latent therapeutic activities, accelerate mechanism-of-action deconvolution, and facilitate the identification of clinically actionable pro-remyelinating therapies.

P057

NUTRACEUTICAL POTENTIAL OF ANCIENT WHEATS: EXPLORING THEIR DISTINCTIVE BIOLOGICAL PROPERTIES

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Wheat is one of the most cultivated cereals worldwide and represents a primary resource for human diet, since it contains different nutrients, amongst them carbohydrates, vitamins and proteins [1]. In recent years, some ancient wheat species attracted the interest of the scientific world because of their promising nutritional and nutraceutical properties [2, 3]. Several studies have suggested a healthier nutritional profile with respect to modern wheat species, mainly because the ancient wheat species contain higher amounts of polyphenols, carotenoids, phytosterols, phenolic compounds and so on [4]. With this in mind, the flours of four different ancient wheat varieties, grown under organic farming conditions, namely Senatore Cappelli (*Triticum turgidum* subsp. *durum*), Gentil Rosso, Verna and Maiorca (*Triticum aestivum*) were extracted using two eco-friendly solvents, *i.e.* ethanol and ethyl acetate. The extracts were subjected to qualitative and quantitative chemical analyses and then used for testing their biological properties. Particularly, they exerted an interesting activity on a panel of cancer cells (*e.g.* MCF-7, MDA-MB-231 and so on), exhibiting a good selectivity with respect to the normal cells. Moreover, the best active extract(s) induced genomic DNA damage and triggered cancer cells death by apoptosis. Finally, the antioxidant and anti-inflammatory properties were investigated as well, using *in vitro* and cell-based assays, revealing an important modulatory role. The obtained outcomes strongly suggest a high nutraceutical potential for the selected ancient wheat varieties (Figure 1), paving the way for future *in vivo* studies.

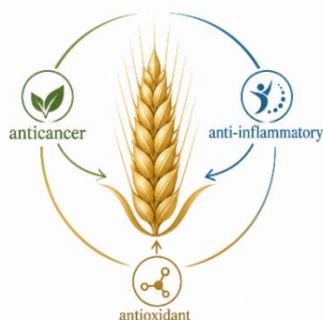


Figure 1. Main biological properties of ancient wheat extracts

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P058

DESIGN, SYNTHESIS AND PRELIMINARY EVALUATION OF NEW CATHEPSIN L INHIBITORS AS POTENTIAL ANTITUMOR AGENTS

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Cathepsin L (CTSL) is a lysosomal cysteine protease that, under physiological conditions, takes part in protein catabolism, tissue remodeling, antigen presentation, and it is also involved in the regulation of cell death and extracellular signaling [1]. In a pathological context, CTSL is involved both in SARS-CoV-2 infection, where it mediates the proteolytic cleavage of the Spike protein, enabling viral entry into the host cell [2], and in tumor progression. Indeed, through the degradation of the extracellular matrix (ECM) and the induction of the epithelial–mesenchymal transition (EMT), its overexpression promotes the proliferation of neoplastic cells and enhances their invasive and metastatic potential [3]. For these reasons, the selective inhibition of CTSL represents a promising therapeutic strategy for the development of new antitumor agents. This work presents the design, synthesis and preliminary pharmacological evaluation of a new series of peptidomimetics as potential CTSL inhibitors. The design was developed starting from **CV13**, an indole-based selective CTSL inhibitor ($IC_{50} = 2.82 \pm 0.76$ nM) previously developed by our research group during studies on SARS-CoV-2 proteases and derived, in turn, from the dual inhibitor **CV11** (Figure 1) [4,5].

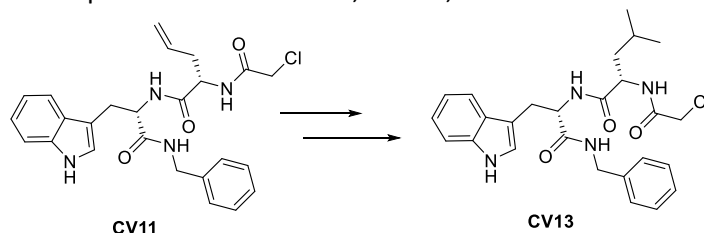


Figure 1. Design of CV13, starting from CV11.

Based on molecular *docking* studies carried out on **CV13**, which highlighted key π – π and hydrogen-bond interactions of the indole core and the benzyl moiety within the binding site of the enzyme, a library of dipeptide analogues bearing an *N*-chloroacetylated leucine was designed and synthesized. The structural modifications involved three positions of the scaffold: the tryptophan residue, the benzyl group and the indole nitrogen at position 1. All compounds were evaluated against CTSL using the *BPS Bioscience Cathepsin L Inhibitor Screening Assay Kit*, using E-64 as the reference inhibitor. Several derivatives showed sub-nanomolar potency, displaying a remarkable inhibitory activity against the protein. The most active compound (**26**), which combines the tryptophan core with a *para*-trifluoromethylbenzyl group, reached an IC_{50} of 0.0033 ± 0.00056 nM, confirming the elevated affinity of the indole scaffold for CTSL and demonstrating that electron-withdrawing substituents on the benzyl moiety markedly increase its activity compared with the electron-donating analogue (**25**, $IC_{50} = 0.023 \pm 0.003$ nM). Therefore, this compound will be subjected to further assays in order to corroborate its potential as an antitumor agent.

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P059

DEVELOPMENT OF GY915, A DUAL KINASE/HDAC INHIBITOR WITH IN VIVO EFFICACY

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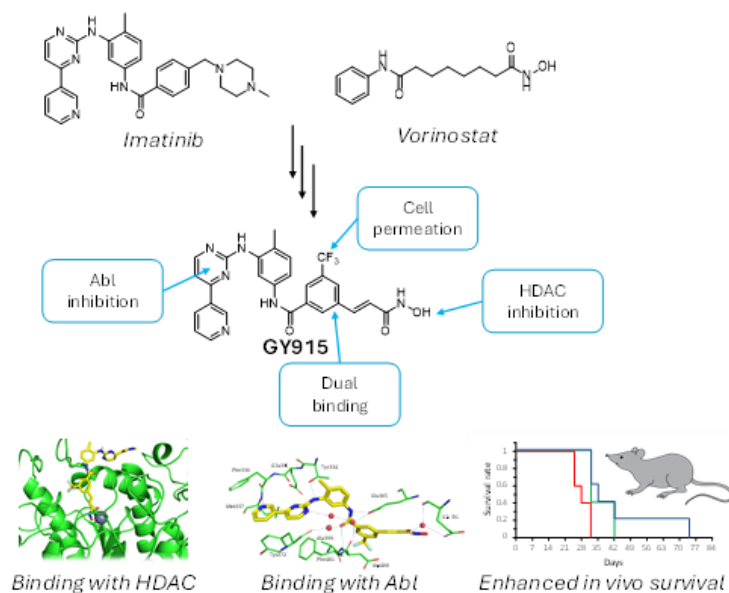
Cancer is a complex and a multiple-genes involved disease; for this reason, it can not be treated or cured with a single drug modulating the biological function of a single target. The innovation related to multi-targeted drugs, combining the activity of different cancer progression relevant targets, became a burgeoning research topic [1]. Drugs that act on multiple targets can enhance efficacy and reduce chemoresistance that causes disease relapse and metastasis and remains the main obstacle to cancer therapy. Tyrosine kinases (TKs) and histone deacetylases (HDACs) are among the major targets in the field of anticancer drugs [2], and several studies demonstrated that co-inhibition of kinases and HDACs produces synergistic anti-leukemic effects, likely by simultaneously disrupting oncogenic signalling and epigenetic repression [3]. Here we present the development of promising dual Abl/HDAC inhibitors endowed with in vivo antileukemia properties (Figure 1).

The design of the first series of chimeric dual Abl/HDAC inhibitors was based on merging the known pharmacophore features for both classes of anticancer drugs.

The hit compounds were then further improved taking into account the SAR emerged from the first series

of compounds as well as pharmacokinetic considerations, yielding the lead **GY915**. The binding mode of the lead compound with the targets was assessed by molecular docking and molecular dynamics simulations.

GY915 potency was assessed against the NCI-60 panel of cancer cell line, providing superior activity than the reference compounds (imatinib and vorinostat). *In vivo* evaluation of GY915 highlighted its efficacy and safety.



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P060

DECODING MYCOBACTERIAL SALICYLATE SYNTHASES: STRUCTURAL CLUES FOR NEW DRUGS

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Tuberculosis and nontuberculous mycobacterial infections remain major global health challenges, further exacerbated by increasing drug resistance and the urgent need for novel antibacterial agents.[1] In this context, the identification of mycobacteria-specific pathways essential for host colonization and survival is crucial for the development of novel therapeutic strategies.

Salicylate synthases (SaS), absent in humans, are key enzymes in mycobacterial siderophore biosynthesis and play an essential role for iron acquisition during host infection, making them attractive targets for antivirulence approaches.[2]

Herein, we show that SaS enzymes from *M. tuberculosis* (Mtb), *M. avium* (Mav), and *M. abscessus* (Mab) display markedly different sensitivities to validated phenyl-furan inhibitors (Figure 1). Notably, Mab SaS is significantly more susceptible, with up to a 10-fold lower IC₅₀ compared to Mtb and Mav orthologues. This occurs despite moderate-to-high sequence identity (64–83%), highlighting how limited sequence divergence can translate into pronounced functional differences.[3-5]

These findings reveal a critical limitation of a "one-size-fits-all" strategy in SaS inhibitors design and emphasize the need to account for species-specific structural features. Targeting these differences may enable the development of both broad-spectrum and precision antimycobacterial therapies.

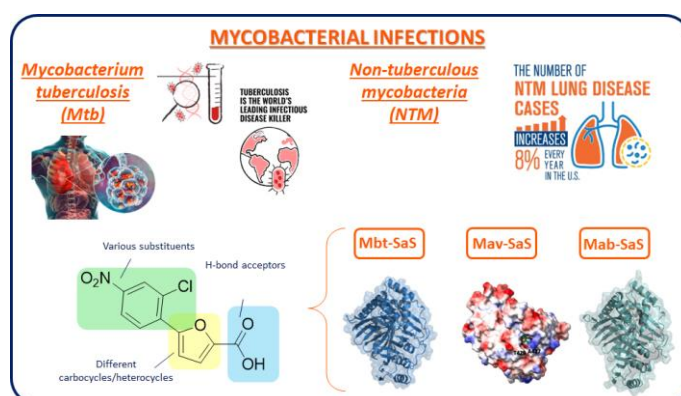


Figure 1. Schematic validated phenyl-furan inhibitors against mycobacterial SaS.

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P061

SANGIOVESE GRAPE SEEDS EXTRACT AS A NUTRACEUTICAL CANDIDATE FOR THE SUPPORT OF CARDIAC AMYLOIDOSIS THERAPY

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The wine industry generates considerable quantities of organic by-products throughout the vinification process, the valorisation of which represents both an environmental imperative and a significant scientific opportunity. In Italy and across major wine-producing regions worldwide, grape pomace constitutes the primary fraction of such waste streams and has attracted increasing interest as a potential source of bioactive molecules with functional and therapeutic relevance. [1][2]

The present work focuses on a polyphenolic extract derived from Sangiovese grape seeds, sourced from ColleMassari estate in the Maremma area of Tuscany, with the aim of characterising its chemical composition and evaluating its biological activity. Chemical characterisation and quantification of the extract were carried out by High-Performance Liquid Chromatography (HPLC), complemented by colorimetric assays for the determination of total polyphenol and total flavonoid content.

Antioxidant capacity was assessed through a multi-method approach encompassing both cell-free radical scavenging assays (DPPH and ABTS) and a tissue-based oxidative stress model using rat tissue homogenate (TBARS). Metal chelating activity was additionally evaluated by UV-Vis spectroscopy. The extract exhibited a well-defined phytochemical profile and consistent antioxidant activity across the methodologies employed. Based on these results, preliminary investigations are currently underway to explore its potential interaction with transthyretin (TTR), a plasma carrier protein whose pathological misfolding leads to the formation and progressive tissue deposition of amyloid fibrils, giving rise to TTR amyloidosis (ATTR). The *in vitro* tests suggest that the bioactive components, present in the extract, bind TTR and stabilize its tetrameric structure preventing the misfolding process. The findings suggest that the extract possesses a biological profile compatible with its use as an active component of nutraceutical supplements intended to support existing pharmacological approaches to ATTR management, providing a rationale for further mechanistic and preclinical investigation.

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P062

SYNTHESIS OF NOVEL 3-PHENOXYPROPAN-2-OL DERIVATIVES AS POTENT AZOLE-BASED HEME OXYGENASE 1 INHIBITORS

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Heme oxygenase 1 (HO-1) is upregulated in response to oxidative and inflammatory stimuli, unlike the constitutively expressed heme oxygenase 2 (HO-2), which plays a key role in physiological heme homeostasis and cytoprotection. While HO-1 exerts an essential protective role in maintaining cellular homeostasis in normal cells, its overexpression in cancer cells has been associated with increased tumor aggressiveness and drug resistance [1]. Preclinical evidence indicates that selective inhibition of HO-1 can sensitize cancer cells to chemotherapy, highlighting HO-1 as a promising therapeutic target. Azole-based inhibitors represent the most relevant class of non-competitive HO-1 inhibitors, with OB-24 serving as a reference compound (Figure 1) [2]. These molecules share key pharmacophoric features, including an azole nucleus capable of coordinating the heme iron, a flexible spacer, and a hydrophobic moiety that stabilizes binding within the enzyme's primary hydrophobic pocket [3]. In this study, a new series of 3-phenoxypropan-2-ol derivatives has been designed and synthesized by employing either imidazole or 1,2,4-triazole rings as the azole nucleus. Structural optimization focused on systematic variation of the hydrophobic moiety (i.e., phenoxy group) combined with a three-methylene spacer chain and the incorporation of a secondary alcohol group (Figure 1). The newly synthesized compounds were evaluated for their inhibitory activity against HO-1, highlighting 1-(4-cyclohexylphenoxy)-3-(1*H*-imidazol-1-yl)propan-2-ol (**2a**) as the most promising inhibitor when compared to the standard OB-24 (IC₅₀ = 3.2 μM vs 8,08 μM, respectively). Finally, binding interactions and structure-activity relationships were elucidated by molecular docking studies.

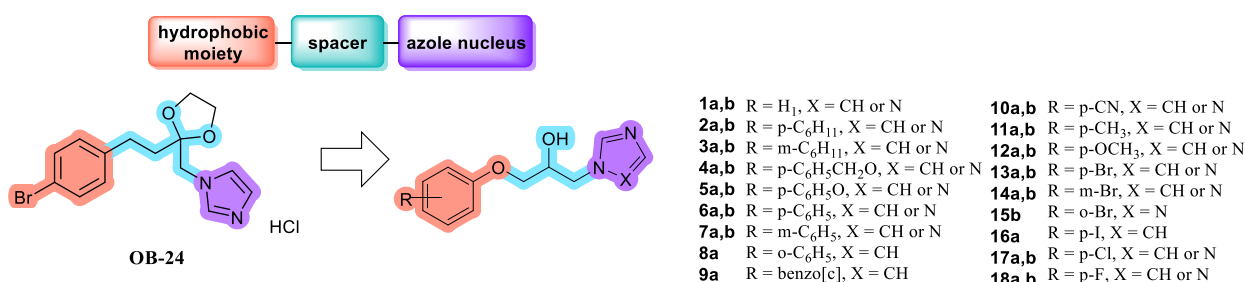


Figure 1. Pharmacophores and general structure of newly synthesized HO-1 inhibitors.

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P063

QUERCETIN ATTENUATES THERMAL BURN-INDUCED INFLAMMATION BY MODULATING PRO-INFLAMMATORY MEDIATORS AND COX/NOS EXPRESSIONS IN RATS

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Thermal skin injury is a debilitating condition characterized by localized tissue damage and the subsequent activation of complex inflammatory cascades. Given that phenolic compounds are recognized for their potent anti-inflammatory properties, this study investigated the protective mechanisms of the flavonoid quercetin (QT) against thermal burn-induced inflammation in a rodent model. Following the induction of thermal burns, subjects were administered QT at dosages of 15, 30, and 60 mg/kg/day for seven days, beginning 24 hours post-injury. Analysis of wounded skin tissue revealed that QT treatment significantly attenuated the elevated levels of pro-inflammatory cytokines and mediators, including TNF- α , IL-6, IL-1 β , LTB₄, and PGE₂, as well as the apoptotic marker caspase-3. Furthermore, RT-PCR and Western blot analyses demonstrated that QT markedly inhibited injury-induced overexpression of mRNA and protein levels of COX-1, COX-2, iNOS, eNOS, and CD31. These findings highlight the potent anti-inflammatory and protective effects of quercetin, suggesting its potential as a therapeutic agent for modulating inflammatory pathways in burn wound management. Future research is warranted to elucidate further the specific molecular mechanisms underlying these therapeutic effects.

Key words: Quercetin, Thermal burn, Inflammation, Cytokines, Cyclooxygenase, Nitric oxide synthase, Rodent model.

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P064

INVESTIGATION OF C(sp²)-C(sp³) NAPHTHOCOUMARIN ATROPISOMERS FOR THE TREATMENT OF ENTEROVIRUS EV-A71 INFECTIONS

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The recent resurgence of Enterovirus A71 (EV-A71) infections, driven by evolving subgenogroups and the lifting of non-pharmaceutical interventions, is currently representing a significant public health challenge [1]. EV-A71 infection causes hand-foot-mouth disease (HFMD), herpangina, fever, but can sometimes induce a variety of neurological complications, including encephalitis, aseptic meningitis, pulmonary edema, and acute flaccid paralysis. Although three EV-A71 vaccines are available in China, they displayed reduced efficacy and limited protection against emerging strains [2]. On the other hand, atropisomerism is becoming extremely relevant in modern drug discovery, but despite its importance, significant amount of work is still required to establish novel synthetic strategies for the development of bioactive molecules endowed with stable stereogenic axes [3]. With this aim, we studied a new class of 2-hydroxy-3-(2-oxochroman-4-yl)naphthalene-1,4-diones obtained through a tandem 1,4-Michael addition/decarboxylation process, evaluating their *in vitro* cytotoxicity and broad-spectrum activity against RNA viruses (figure 1) [4]. Compound **3k** displayed compelling anti-EV-A71 activity combined with a great safety profile on mock-infected cells. Further cell-based assays highlighted its possible interaction during early events of the EV-A71 replication cycle. In parallel, using an organocatalytic approach, the scope of the reaction has been expanded achieving enantiomerically enriched compounds and a configurationally stable C(sp²)-C(sp³) synclinal atropisomer, providing an innovative toll for the synthesis of complex molecules with defined stereochemical features and potential pharmaceutical applications.

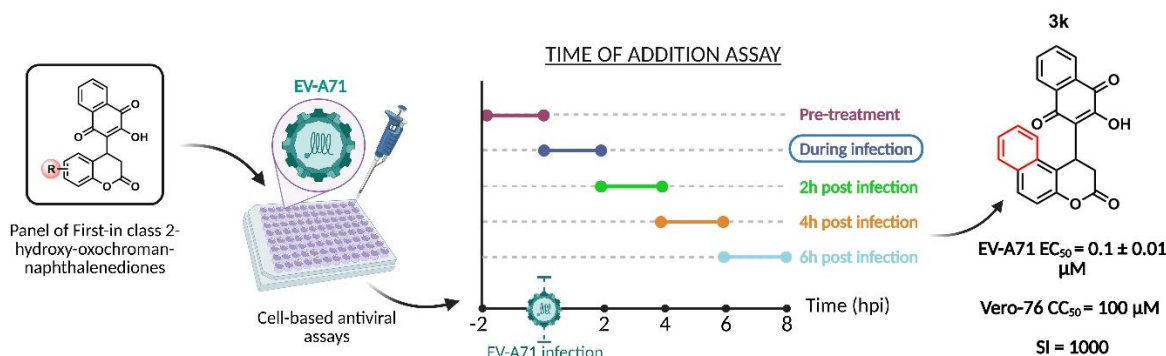


Figure 1. Synthesis and antiviral activity of a new class 2-hydroxy-oxochroman-naphthalenediones.

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P065

THE PyRMD STUDIO ADVANCEMENT: AN ACCESSIBLE AI-POWERED PLATFORM FOR ULTRA-LARGE VIRTUAL SCREENING

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The integration of Artificial Intelligence (AI) into virtual screening (VS) campaigns has fundamentally shifted modern drug discovery, enabling the rapid exploration of ultra-large chemical libraries containing billions of compounds (e.g., the Enamine REAL database).^{1,2} In turn, the screening of massive compound libraries significantly enhances the potential for identifying novel and potent drug candidates, a result often unattainable with smaller sets.^{3,4} However, the widespread adoption of AI-powered VS tools is often hindered by three major challenges: the need for substantial resources and specialized software,⁴ the steep learning curve associated with command-line interfaces, and the prevalence of a phenomenon known as "data leakage".⁵ Specifically, this is a critical bias caused by improper data splitting that leads to falsely optimistic model performance and misdirects real-world drug discovery efforts.⁶

To overcome these limitations, we introduce PyRMD Studio, a comprehensive update that unifies our previous Ligand-Based (PyRMD)⁷ and Structure-Based (PyRMD2Dock)⁸ screening tools into a single platform. PyRMD Studio features an intuitive Graphical User Interface (GUI) compatible with both Windows and Linux, specifically designed to democratize access to sophisticated AI workflows for non-expert users without requiring coding expertise.

Crucially, PyRMD Studio addresses data leakage by implementing a rigorous validation strategy. By combining Butina clustering with a cross-validation adapted Stratified GroupKFold splitting approach, the software ensures a strict structural separation between training and test sets. While this robust mitigation strategy yielded an expected, yet far more realistic average F-score reduction of 9% during benchmarking experiments, it successfully prevents the models from overfitting to specific structural motifs.

Furthermore, extensive code refactoring and vectorization have significantly enhanced computational efficiency, resulting in an approximate 3.3-fold increase in screening speed compared to its predecessor, enabling the screening of 1 million compounds in roughly 60 minutes. Ultimately, PyRMD Studio provides the scientific community with a fast, transparent, and highly accessible toolkit to streamline modern hit identification campaigns.

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P066

DEVELOPMENT OF PHOTOSWITCHABLE LIGANDS FOR THE MODULATION OF THE GPR120 RECEPTOR

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The G protein-coupled receptor GPR120 (FFAR4) plays a pivotal role in the regulation of energy metabolism and glycaemic homeostasis, making it a primary therapeutic target for Type 2 diabetes mellitus (T2DM) and obesity. Furthermore, it is involved in neuroprotective processes, appetite regulation, and the enhancement of wound healing. Mutagenesis and molecular modelling studies have identified critical determinants for ligand-receptor interaction: the residues Arg99 and Arg178 serve as essential anchoring points for establishing electrostatic interactions with the polar head of ligands. Complex stability is further ensured by a hydrophobic pocket defined by key residues such as Arg99, Trp277, Phe304, and Phe311, which accommodate the aromatic moieties or aliphatic chains of the most potent agonists [1]. In this study, we have designed a new series of photoswitchable ligands aimed at achieving optical and dynamic control over GPR120 signalling. The selected photo-isomerizable scaffold is known for its optimal photochemical properties and conformational rigidity [2]. Ligands were designed with a terminal carboxylic acid group for specific interaction with Arg99. The structure was appropriately functionalized with aromatic substituents to optimize hydrophobic contacts with residues Phe304, Phe311, and Trp277, identified as critical for ligand stabilization within the lipophilic pocket (Figure 1). Biological characterization includes cytotoxicity

evaluation and receptor affinity assays for GPR120 to validate the molecular design. The evaluation begins with the synthetically obtained pure *E*-isomer, as the thermodynamically stable form, to establish the basal activity profile. Finally, the photostationary mixture (PSS), resulting from photo-isomerization, will be tested to analyze how light-induced conformational variations influence interactions with key residues and receptor activation efficacy, confirming the potential of photoswitches as innovative tools for GPR120 research and therapy.

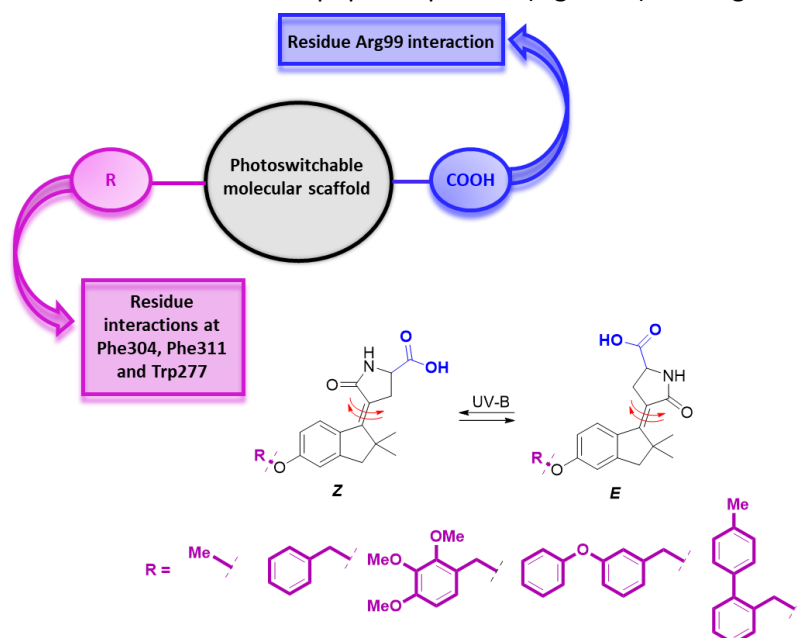


Figure 1. Rational design and light-dependent modulation of photoswitchable ligands targeting the GPR120 receptor.

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P067

SYNTHESIS AND FUNCTIONALIZATION OF PYRAZOLO[3,4-d]PYRIMIDINE DERIVATIVES AS POTENTIAL Src KINASE INHIBITORS

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Src is a non-receptor tyrosine kinase critically involved in tumor progression, metastasis, and therapeutic resistance. Its aberrant activation has been documented in several aggressive malignancies, including triple-negative breast cancer, glioblastoma, and pancreatic cancer, thus representing a valuable molecular target for anticancer drug development. Among heterocyclic scaffolds, pyrazolo[3,4-d]pyrimidines have emerged as privileged structures in kinase inhibition. Prototypical compounds such as PP1 and PP2 have historically served as reference inhibitors, while more recent derivatives SI306⁽¹⁾ and SI113⁽²⁾ have demonstrated potent and selective activity against Src-related pathways. Building on these findings, the present study explores the design and synthesis of novel analogues aimed at expanding the structure–activity relationship landscape of this class. A focused library of pyrazolo[3,4-d]pyrimidine derivatives (Figure 1) was synthesized via a multistep strategy involving the preparation of key intermediates from styrene oxide precursors, followed by cyclization to afford the core heterocyclic framework. Subsequent regioselective functionalization at positions 4 and 6 enabled structural diversification and fine-tuning of physicochemical properties. Notably, the introduction of allyl moieties at position 6 was investigated as a versatile handle for conjugation with nanocarriers, such as halloysite nanotubes⁽³⁾, with the objective of enhancing drug delivery and bioavailability in vivo. The synthesized compounds are currently undergoing biological evaluation, including enzymatic inhibition assays and antiproliferative studies in cancer cell models. Preliminary results are expected to provide insights into their therapeutic potential as next-generation Src kinase inhibitors.

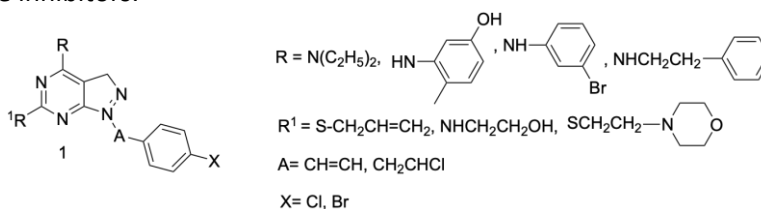


Figure 1. General structure of the synthesized pyrazolo[3,4-d]pyrimidine derivatives.

References:

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P068

SUSTAINABLE SYNTHESIS AND BIOLOGICAL EVALUATION OF TACRINE-LIKE MULTI-TARGET HYBRIDS AS ANTI-ALZHEIMER CANDIDATES

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The complex and multifactorial etiology of Alzheimer's disease (AD) imposes a severe socioeconomic burden and highlights the limitations of current therapeutic options, which are mainly confined to symptomatic drugs or monoclonal antibody-based therapies with restricted eligibility and relevant adverse effects [1,2]. To overcome these limitations and address the multiple pathways involved in neurodegeneration, the development of multi-target-directed ligands (MTDLs) has emerged as a key paradigm in modern drug discovery [3].

In this framework, we report the design and synthesis of a novel library of MTDL hybrids combining a tacrine core, selected for its well-established anticholinesterase properties, with bioactive aryloxy-methylene scaffolds (Figure 1). Although initial synthetic efforts relied on conventional procedures, the methodology was successfully re-engineered according to green chemistry principles. In particular, the use of deep eutectic solvents (DESs) markedly improved reaction efficiency and sustainability, aligning the synthetic workflow with eco-friendly standards.

In vitro enzymatic screening demonstrated that all synthesized derivatives exerted potent dual inhibition against both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Furthermore, structure-activity relationship (SAR) analysis revealed that the electronic and steric features of the substituents on the aryloxy ring critically modulate both inhibitory potency and selectivity.

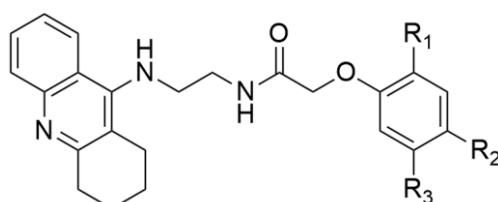


Figure 1

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- [3] Piemontese L. *et al. Front. Clin. Drug Res. - Alzheimer Disord.* **2019**, 8, 33 - 80.

P069

NADES-BASED GREEN EXTRACTION OF GRAPE POMACE POLYPHENOLS: A SUSTAINABLE APPROACH TO NOVEL DIETARY SUPPLEMENTS

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In the Mediterranean area, grape is one of the main cultivated fruit crops and is mostly used in winemaking, a process that generates large amounts of by-products, mainly consisting of grape pomace [1]. Due to its well-known richness in bioactive compounds and its relevant properties, including strong radical-scavenging power and antimicrobial activity, grape pomace may represent a valuable secondary raw material to be reused as a resource [1,2].

In the present work, natural deep eutectic solvents (NADESs) were used to extract polyphenols from different varieties of grape pomace collected in Apulia, Italy [2]. After a preliminary HPLC-DAD screening, selected samples were further investigated through LC-QTOF-MS metabolomic characterization. In particular, conventional Sangiovese and organic Merlot grape pomaces extracted with betaine hydrochloride/lactic acid 1:4, mol/mol + 40% water, Bet/LA, and choline chloride/ascorbic acid 2:1, mol/mol + 40% water, ChCl/AA, were analyzed [2].

The results showed that betaine-based extracts, from both cultivars, achieved approximately three-fold higher polyphenol recovery. Further analyses also revealed higher antimicrobial activity and good antioxidant power for these extracts [2]. For this reason, subsequent *in vitro* digestion experiments were carried out on Bet/LA extracts, with metabolomic profile, antioxidant activity, and total polyphenol content determined in each digestion phase. Glycoside content increased up to the duodenal phase, followed by an enrichment of free polyphenols during the colon phase, probably due to the metabolic activity of lactic acid bacteria.

The introduction of *Lactobacillus plantarum* from the beginning of the experiments significantly reduced the original grape pomace-like polyphenols, while maintaining high antioxidant activity and total phenolic content, suggesting the formation of new probiotic-derived compounds. Together with further results from dietary supplementation studies in quails, these findings support the potential use of NADES-based grape pomace extracts in supplement formulations with nutraceutical properties.

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Nuove Prospettive in Chimica Farmaceutica

P070

MAPPING THE CONFORMATIONAL LANDSCAPE OF HuR: AN IN SILICO STUDY ON THE IMPACT OF PHOSPHORYLATION SITES

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The RNA-binding protein HuR (ELAVL1) is a ubiquitous key post-transcriptional regulator responsible for stabilizing mRNAs encoding growth factors, cytokines, pro-inflammatory enzymes, and mediators of the cell cycle and apoptosis. The overexpression and persistent cytoplasmic localization of HuR are hallmarks in the pathogenesis of numerous malignancies, positioning this protein as a promising target in anticancer therapy. Structurally, HuR comprises three highly conserved RNA recognition motifs (RRM1-3). The biological activity and nucleocytoplasmic shuttling of the protein are finely orchestrated by post-translational modifications, among which site-specific phosphorylation by various kinases plays a prominent role. Residues located within the RRM1 and RRM2 domains (such as Ser88, Ser100, and Thr118) directly modulate the binding affinity for target RNAs, thereby conditioning the stability of transcripts linked to proliferation and survival. Conversely, modifications in the hinge region and the RRM3 domain (such as Ser221 and Ser318) govern nucleocytoplasmic translocation in response to stress stimuli [1-3]. Despite the crucial role of these modifications, the atomistic and molecular details through which phosphorylation alters the conformation and structural dynamics of HuR remain largely elusive. Characterizing the conformational impact induced by these biochemical events is therefore essential for the rational drug design of next-generation inhibitors. The present study aims to explore the structural landscape of HuR using in silico computational approaches. Through molecular dynamics (MD) simulations, we will evaluate the impact of both known phosphorylation profiles and potentially novel modification sites on the protein's flexibility and conformational rearrangements, laying the groundwork for the identification of allosteric pockets exploitable for therapeutic purposes. This work was funded by the BEN-HUR Project (CUP No. E43C24000230005).

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P071

PHARMACOKINETIC CHARACTERIZATION THROUGH INTEGRATED DMPK/PK APPROACHES FOR ANTI-INFLAMMATORY MOLECULES

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Early characterization of pharmacokinetic and metabolic properties is essential for the successful development of new chemical entities [1]. In this study, a comprehensive *in vitro-in vivo* drug metabolism and pharmacokinetics/ pharmacokinetics (DMPK/PK) assessment was performed to characterize compound 11, a promising anti-inflammatory lead compound.

The DMPK profile of compound 11 was investigated through plasma stability, plasma and microsomal protein binding, metabolic stability in human liver microsomes, metabolite identification, glutathione trapping experiments, and hepatic clearance prediction using *in vitro-in vivo* extrapolation (IVIVE). In addition, *in vivo* pharmacokinetic studies were conducted in mice using a validated LC-MS/MS bioanalytical method.

Compound 11 displayed high stability in human plasma and moderate metabolic turnover in human liver microsomes. Metabolic investigations demonstrated that CYP-mediated oxidation represents the predominant biotransformation pathway, while glucuronidation contributes to a lesser extent. Metabolite identification studies revealed the formation of two oxidative metabolites and one glucuronide conjugate, with consistent metabolite profiles observed in both *in vitro* and *in vivo* experiments. Time-course analyses indicated progressive metabolite formation, with one oxidative metabolite emerging as the major biotransformation product. Furthermore, no glutathione conjugates were detected, suggesting a low propensity for the formation of reactive metabolites.

Integration of metabolic stability and protein-binding data enabled the prediction of hepatic clearance and provided insights into the relative contribution of the main metabolic pathways. Pharmacokinetic evaluation in mice demonstrated measurable systemic exposure and confirmed the presence of the principal circulating metabolites identified during *in vitro* studies.

Overall, these findings provide a comprehensive understanding of the metabolic fate and pharmacokinetic behavior of compound 11 and support its further development as a potential anti-inflammatory drug candidate.

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P072

COMPUTATIONAL DESIGN AND SYNTHESIS OF CANDIDATE DUAL INHIBITORS TARGETING ADAM17 AND KRas-G12C AGAINST NSCLC

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Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality, with treatment frequently limited by acquired resistance.¹ KRas is one of the most common oncogenic drivers in NSCLC, and the G12C variant represents a major therapeutic target.² However, resistance to KRas-G12C inhibitors commonly emerges through secondary mutations and activation of compensatory signalling pathways, several of which are regulated by A Disintegrin and Metalloproteinase 17 (ADAM17).^{3,4} Simultaneous modulation of KRas-G12C and ADAM17 may therefore provide a strategy to prevent or overcome resistance. On these premises, in this study, we developed a strategy to design the first KRas-G12C/ADAM17 dual inhibitors (Figure 1). First, ADAM17 and KRas-G12C inhibitors were retrieved from public literature and clustered into structurally diverse scaffold families. Ligand-based similarity screenings were then combined with application of machine learning model classifiers for predicting target inhibition and antiproliferative activity against selected NSCLC cell lines. Besides, structural analysis of ADAM17 and KRas-G12C ligand-bound crystal structures reported into the Protein Data Bank enabled the selection of representative protein conformations for docking and interaction-based prioritization. Based on the computational results, a focused library of structurally related compounds was then designed, and synthesized. Preliminary biological evaluation against ADAM17 and KRas-G12C targets are currently ongoing. Overall, this work establishes a computationally driven framework for developing single molecules potentially capable of simultaneously modulating KRas-G12C and ADAM17 in drug-resistant NSCLC.

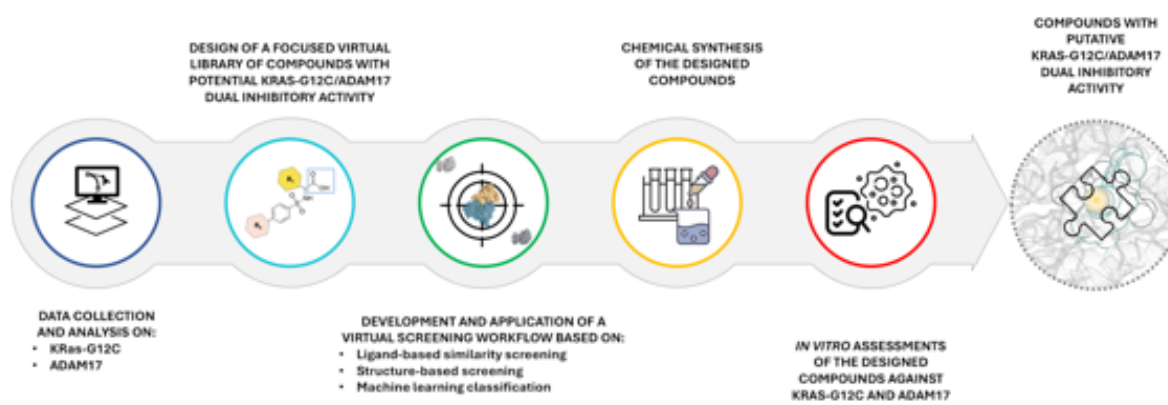


Figure 1. Workflow adopted in this study.

References:

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P073

IDENTIFICATION OF CHLORMIDAZOLE AS A REPURPOSING CANDIDATE AGAINST AGGRESSIVE PROSTATE CANCER THROUGH CHEMOINFORMATICS AND MACHINE LEARNING

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Advanced and metastatic prostate cancer (PC) are among the most difficult types of tumours to treat, particularly after resistance to standard therapies develops.¹ Drug repurposing can accelerate the discovery of new therapeutic options, but computational screening is often hampered by false-positive predictions and limited model applicability.²

In this work, we developed and prospectively validated an integrated workflow combining ligand-based similarity, applicability-domain assessment, and machine learning (ML) classification (Figure 1). Evaluation of the developed models on independent external datasets confirmed that restricting predictions to relevant chemical space improved hit enrichment, reduced false positives, and increased overall screening reliability.

Application of the developed workflow to DrugBank allowed the identification of five compounds with antiproliferative activity in selected PC cell lines, in both 3D tumour spheroids and 2D PCa cell lines with distinct androgen receptor signalling profiles.^{3,4} Among them, Chlormidazole emerged as the most promising candidate. It produced predominantly cytostatic effects in PC cells, accompanied by increased p57 expression, reduced Rb phosphorylation, and G1 cell-cycle arrest. Chlormidazole also enhanced docetaxel activity in both 2D and 3D models, allowing similar efficacy at lower docetaxel concentrations. Collectively, these findings support chlormidazole as a potential repurposing candidate for prostate cancer and demonstrate the value of combining chemoinformatics, ML, and applicability-domain control in virtual screenings.

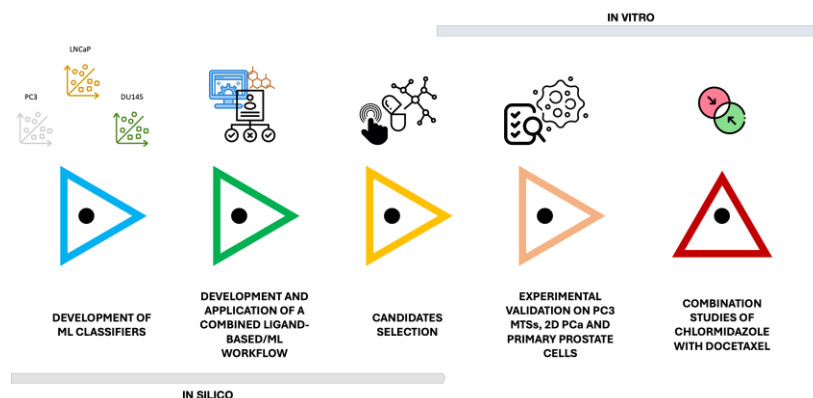


Figure 1. Workflow adopted in this study.

References:

- [1] Zhang, S. *et al. Drug Discov Today*. **2025**, 30(6), 104384. [2] Keramida, P. *et al. Medicines (Basel)* **2025**, 12(4), 28.
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P074

NOVEL α -GLUCOSIDASE INHIBITORS BASED ON BENZIMIDAZOLE CORE STRUCTURE: FROM SYNTHESIS TO COMPUTATIONAL STUDIES

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Type 2 diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance and persistent hyperglycemia, which leads to cardiovascular diseases, retinopathy, and neuropathy. Among the available therapeutic strategies, inhibition of α -glucosidase represents a well-established approach for controlling postprandial blood glucose levels. However, FDA-approved α -glucosidase inhibitors are frequently associated with various side effects, including bloating, flatulence, diarrhea, abdominal discomfort, highlighting the urgent need for the development of novel and safer antidiabetic agents. [1,2] In recent years, several benzimidazole derivatives have attracted considerable attention in medicinal chemistry due to their promising antidiabetic properties. [3]. Herein, a series of novel benzimidazole derivatives was synthesized, characterized, and evaluated against α -glucosidase. Among them, several compounds demonstrated significant inhibitory effects and showed no cytotoxicity at the tested concentrations. To rationalize the experimental findings and guide the optimization of the chemical analogues, an integrated computational workflow was developed. (Figure 1)

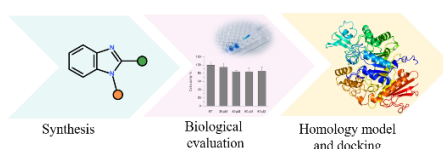


Figure 3. Schematic representation of the study workflow.

Since the crystallographic structure of the target protein was unavailable, a homology model of α -glucosidase was first generated and structurally validated. Subsequently, the binding cavity was characterized to identify the key residues involved in ligand recognition and stabilisation. Molecular docking studies were then carried out to investigate the binding modes and interaction profiles of the most active synthesized compounds within the catalytic site. Finally, molecular dynamics simulations were performed to assess the stability and dynamic behaviour of the most promising protein-ligand complexes.

Overall, the proposed computational strategy provides valuable insights into the potential of benzimidazole derivatives as α -glucosidase inhibitors and may support the rational design of newer benzimidazole-based derivatives with improved antidiabetic potential.

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P075

THE SUBSTRATE REDUCTION APPROACH FOR THE TREATMENT OF GAUCHER DISEASE: DESIGN AND DEVELOPMENT OF NOVEL GLUCOSYLCERAMIDE SYNTHASE INHIBITORS

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Gaucher disease (GD) is the most common among the Lysosomal Storage Diseases (LSDs), a heterogeneous group of rare diseases, and is caused by a deficiency of the lysosomal enzyme Glucocerebrosidase (GCase), resulting in the accumulation in the lysosomes of its unmetabolized substrates, glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph)¹. Systemic administration of recombinant GCase is the main therapeutic option but it lacks efficacy in tackling neuropathic symptoms, due to enzyme inability to cross the BBB². To prevent its accumulation, the synthesis of GlcCer could be decreased by inhibiting the activity of the glucosylceramide synthase (GCS), responsible for the biosynthesis of GlcCer. This represents an attractive therapeutic strategy for GD based on the development of small molecules as GCS inhibitors³, the chemo-physical properties of which can be finely tuned for an efficient delivery in the CNS.

A ligand-based approach has been carried out taking as reference compound T-036, a previously reported GCS inhibitor⁴. A virtual screening of commercially available libraries of compounds has been performed using the software FLAP⁵ which led to the identification of 22 novel potential GCS inhibitors.

Biological evaluation of the selected compounds by mean of a preliminary cell-based assay, using Hek GBA1 KO cells, demonstrated that 3 molecules out of 22 reduced the cellular levels of GlcSph to an extent comparable to the reduction induced by eliglustat tartrate, a GCS inhibitor approved by FDA for the treatment on non-neuropathic GD.

A 3D model of GCS has been generated according to previously reported structural information⁶. Molecular docking simulations highlighted a common mode of occupation of the proposed binding pocket for the reference compound T-036 and for the active compounds.

In summary, a ligand-based drug discovery approach has been carried out to identify novel GCS inhibitors for the treatment of GD. Some candidates, with different chemotypes, were able to reduce the intracellular levels of GlcSph in the Hek GBA1 KO cells. The selected molecules represent three novel potential lead compounds that will guide the design and the development of more potent GCS inhibitors.

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P076

MULTITARGET-DIRECTED LIGANDS TARGETING VIRAL PROTEASES AND HUMAN CATHEPSIN L AGAINST SARS-CoV-2

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Multitarget-directed ligands (MTDLs) represent a powerful strategy to address complex multifactorial diseases by simultaneously modulating multiple biological targets involved in disease progression.[1] The multifactorial nature of SARS-CoV-2 infection, involving both viral replication pathways and host cellular responses, highlights the potential advantages of multitarget inhibitors, which may simultaneously modulate different mechanisms of disease progression, thereby enhancing antiviral efficacy and reducing the emergence of drug resistance.[2]

In 2025, Fattorusso *et al.* reported novel 1,2,4-thiadiazolidin-3,5-diones as multitarget inhibitors of SARS-CoV-2 main protease (M^{pro}), SARS-CoV-2 papain-like protease (PL^{pro}), and human cathepsin L (hCatL), which are involved in viral infection.[3] Meanwhile, several studies described potent protease inhibitors, in which the roles of the warheads and peptide-based binding regions have been elucidated.[4-5]

Starting from this finding, we developed a new series of 18 hybrid compounds (**SPR142-159**, Figure 1) carrying a vinyl (methyl or benzyl) ester warhead and different substituted 2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetyl moieties, which could mimic the core of lead compounds. These two fragments were linked through a Gln pentatomic surrogate, norvaline, and β Ala-Gly/Gly- β Ala spacers, rationally incorporated since correspond to favorite residues of M^{pro}, hCatL, and PL^{pro}, respectively, at the P1 site.

Biological properties against viral targets and hCatL have been assessed.

Selectivity assays, antiviral activity, cytotoxicity, and *in silico* studies of the most promising inhibitors are currently being investigated.

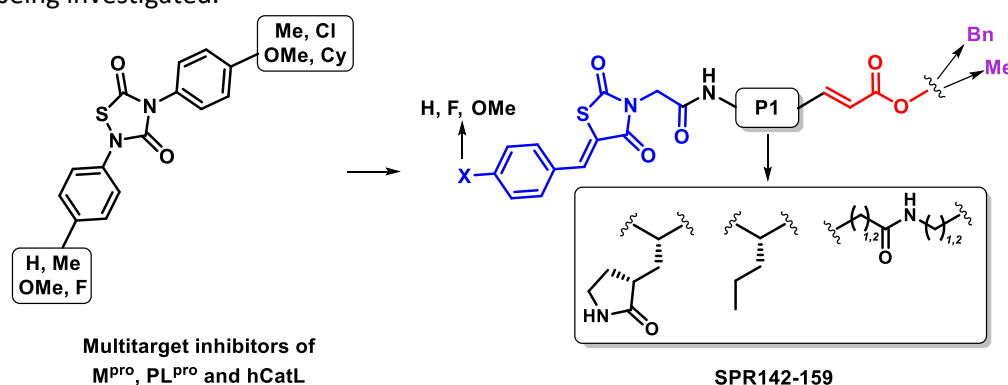


Figure 1. Design of new hybrid peptidomimetics **SPR142-159**.

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P077

DEVELOPMENT OF SELECTIVE HUMAN CATHEPSIN L INHIBITORS WITH ANTI-GLIOBLASTOMA PROPERTIES

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Human cathepsin L (hCatL) is markedly upregulated in glioblastoma and has been associated with enhanced tumor invasiveness, extracellular matrix degradation, angiogenesis, and resistance to apoptosis and conventional therapies.[1] Its involvement in multiple pathways related to tumor progression and poor patient prognosis highlights it as a promising therapeutic target.

Starting from the calpain inhibitor XII (**Figure 1**), a potent hCatL inhibitor,[2] a new series of 20 peptide-based Michael acceptors was developed (**SPR122-141**). In particular, the α -keto amide warhead was replaced by vinyl methyl ester, acrylic portion, and vinyl amide moieties, the latter carrying unsubstituted, 4-F, or 4-OMe benzyl rings. At the P1 and P2 sites, norvaline (Nva) and Leu have been alternated with the superior homologous norleucine (Nle) and Phe, respectively. Cbz as the N-cap was maintained.

At the biological investigation towards hCatL, potent inhibitory properties in the nanomolar range were observed for vinyl methyl ester derivatives. Surprisingly, two acid analogues showed significant binding affinities, with K_i values in the sub-micromolar range. The presence of vinyl amide warhead with 4-F-benzyl group was found to be productive, whereas, the incorporation of unsubstituted benzyl and 4-OMe-benzyl moieties led to a modest loss of affinity.

A significant selectivity towards hCatL over hCatB was observed.

In cell-based assays using glioblastoma U87 cells, **SPR128** and **SPR134** showed remarkable antiproliferative effects at 50 μ M, where they induced a pronounced reduction in tumor cell viability, much higher than temozolomide (positive control) used at 100 μ M.

Both compounds were found to be completely inactive on the L-929 control cell line.

In speciation study, the distribution of acid analogue **SPR128** at pH = 5.0, which corresponds to lysosomal pH where hCatL is located, was determined for the 13% as -COOH and 87% in the fully deprotonated form.

In silico studies clarified the binding poses of most potent hCatL inhibitors.

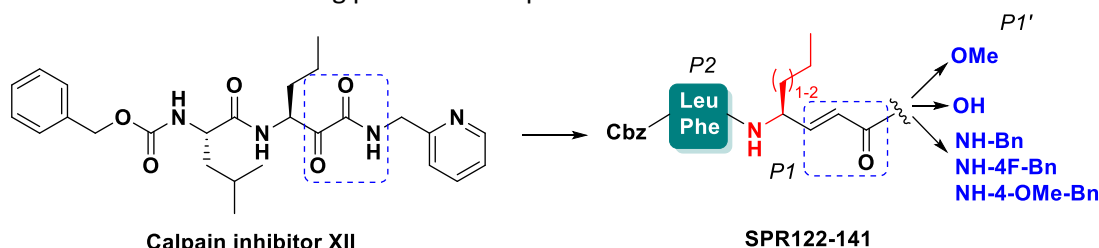


Figure 1. Design of novel SPRs starting from calpain inhibitor XII.

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P078

Pin1 INHIBITION BY atRA-INSPIRED ANALOGUES: AN INTEGRATED AND MINIATURISED ANALYTICAL APPROACH FOR STABILITY PROFILING IN ANTICANCER DRUG DISCOVERY

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Prolyl isomerase Pin1 has emerged as a compelling therapeutic target in oncology, given its central role in regulating tumour-promoting signalling pathways and mediating resistance to conventional anticancer agents. Among the chemical strategies investigated for its inhibition, all-trans retinoic acid (atRA) analogues represent a structurally distinct and pharmacologically relevant class, whose development requires rigorous characterisation of chemical and metabolic behaviour at the early stages of the discovery pipeline [1].

In this work, we report the design, development, full validation and application of an original, miniaturised analytical platform based on Stop-And-Go Extraction (StAGE) tips coupled to UHPLC and mass spectrometry, for the comprehensive stability profiling of a series of atRA-inspired Pin1 inhibitors developed within a multidisciplinary project. Stability was evaluated across multiple relevant environments, including aqueous buffers and organic solvents, cell-culture media and human liver microsomal systems, providing essential physicochemical and metabolic parameters to guide hit prioritisation and lead optimisation decisions [2]. The analytical workflow enabled high-throughput assessment from microlitre-scale sample volumes, ensuring compatibility with the limited material availability typical of early-stage medicinal chemistry programmes [3]. Integration with high-resolution mass spectrometry further supported the structural elucidation of degradation and metabolic products, yielding mechanistic insight into the liability profiles of individual candidates. The results demonstrate how a fit-for-purpose miniaturised analytical infrastructure can meaningfully accelerate compound progression decisions in a multidisciplinary drug discovery context, with direct applicability to other target-ligand systems of medicinal chemistry interest.

This research was supported by National Recovery and Resilience Plan (PNRR), Mission 4 Component 2 Investment 1.1 - PRIN 2022 PNRR of the Italian Ministry of University and Research with European Union - NextGenerationEU funds, Project PRIN-UNO (P2022ZWY8H).

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P079

MULTIVALENT PIPERIDINE-BASED β -GLUCOSIDASE INHIBITORS FOR OVERCOMING CHEMORESISTANCE IN BREAST CANCER THERAPY

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Chemoresistance remains a significant challenge in breast cancer therapy, often leading to treatment failure and recurrence. β -Glucosidase, an enzyme involved in various cellular processes including glycosphingolipid metabolism, has emerged as a potential target in overcoming this resistance [1]. Aberrant glycosylation patterns in cancer cells, often influenced by β -glucosidase activity, contribute to chemoresistance mechanisms [2]. Iminosugars, as potent β -glucosidase inhibitors, offer a promising strategy [3]. By modulating β -glucosidase activity, these compounds can disrupt pro-survival pathways, restore chemosensitivity, and enhance the efficacy of existing chemotherapeutic agents, presenting a novel avenue for improving breast cancer treatment outcomes.

Several monovalent and multivalent iminosugars were synthesized and their inhibitory efficacy against β -Glucosidase was assessed in vitro. MTT vitality assays were conducted using MCF-7 (human breast cancer), C6 (rat glioma), MDA-MB-231 (triple-negative breast cancer), and 3T3 (fibroblast) cell lines, which express β -glucosidase at different levels. Cells were treated with cisplatin, the iminosugars, or a combination of both, to investigate potential synergistic effects. For control purposes, we also tested conduritol- β -epoxide (CBE), a well-established covalent β -glucosidase inhibitor.

Piperidine-based divalent and trivalent iminosugars with a central aromatic scaffold demonstrated promising inhibitory efficacy against β -glucosidase. More notably, a synergistic effect was observed when these iminosugars were co-administered with cisplatin.

Preliminary cellular experiments provided evidence that multivalent iminosugars hold promise as agents to overcome cellular resistance to cisplatin.

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P080

IDENTIFICATION OF NEW ANTIMICROBIAL COMPOUNDS IN ENVIRONMENTAL BACTERIA: A MULTIDISCIPLINARY APPROACH AGAINST RESISTANT PATHOGENS

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Antimicrobial resistance represents a critical challenge for current and future generations, and it is driven by the emergence of resistant pathogens paralleled by the declining efficacy of traditional antibiotics. Thus, there is an urgent need for novel antimicrobial agents that may improve therapeutic outcomes [1]. However, both nature-derived and synthetic compounds developed to date show limitations, and innovative sources for novel scaffolds are being investigated [2]. In this connection, microorganisms may provide a structurally and functionally diverse library of biomolecules, as many species produce antimicrobial compounds in response to external stimuli [1,2].

The collaboration with the University of Zaragoza, in the context of the MicroMundo and MOSAICOH projects [3], the latter being funded by the "UNITA - universitas montium" alliance, allowed the isolation of soil bacterial strains which were screened against a panel of pathogens, including resistant species. For the most active isolates, whole-genome sequencing is being performed to identify biosynthetic gene clusters associated with secondary metabolite production. Such compounds, that include siderophores and peptide-like small molecules with chemically diverse functional groups, are being investigated through a computational drug discovery approach using both ligand-based tools and molecular docking to rationalize *in vitro* data.

The future perspectives of this study include the analytical profiling of strain extracts by means of mass spectrometry and nuclear magnetic resonance and the isolation of the most promising compounds highlighted by *in vitro* tests and computational results.

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P081

UNLOCKING THE ORPHAN RECEPTOR GPR183: AI-DRIVEN DISCOVERY OF NOVEL LIGANDS

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G protein-coupled receptors (GPCRs) represent a dynamic superfamily of therapeutic targets, yet the discovery of modulators for orphan receptors like GPR183, a key regulator of immune cell migration, is hindered by limited chemical scaffold diversity and complex activation mechanisms. Here, we present the discovery of **78**, a novel pyrazolopyridazinone-based GPR183 inverse agonist. This was achieved through PyRMD2Dock¹, an innovative hybrid AI-driven workflow combining the Ligand-Based Virtual Screening (LBVS) tool PyRMD² (centered on the Random Matrix Discriminant) with AutoDock-GPU.³ By training the RMD algorithm on large-scale docking datasets, we rapidly screened ~10 million compounds. Notably, the high structural novelty of the screened library compared to the training data allowed the PyRMD classification to efficiently prioritize a large number of diverse, high-probability binders, leading to the identification of compound **78**.

We rigorously validated **78**'s pharmacological profile using orthogonal biophysical assays. To overcome the lack of robust binding assays for GPR183, a BRET-based conformational biosensor was engineered.⁴ This enabled real-time monitoring of ligand-induced structural rearrangements in living cells, confirming **78**'s direct receptor engagement. Extensive all-atom Molecular Dynamics (1.5 μ s) and Targeted MD elucidated the atomistic basis of the inverse agonism. Simulations revealed a critical "hand-off" mechanism where **78** engages Y260^{6,51} in the orthosteric pocket, disrupting the pivotal Y112^{3,33}-Y260^{6,51} inter-helical lock. This interaction facilitates the relocation of transmembrane helix 3 (TM3), driving the receptor into an inactive conformation. Site-directed mutagenesis experimentally validated this model: the Y260F^{6,51} mutation inverted **78** from an inverse agonist to a partial agonist, confirming the residue as a molecular switch for signal transduction.

Phenotypic studies in primary human cells confirmed the biological relevance of these findings. **78** effectively inhibited constitutive and agonist-induced Gi signaling and β -arrestin recruitment. Crucially, it blocked the chemotaxis of human peripheral blood mononuclear cells (PBMCs), specifically CD4⁺ T and B cells, with a potency matching the reference NIBR189. Validating PyRMD2Dock for exploring vast chemical spaces, this work delivers a potent GPR183 modulator, a new biosensor, and deep mechanistic insights, opening new avenues for cancer, immune, and inflammatory disease therapeutics.

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P082

**DESIGN, SYNTHESIS, AND CHARACTERIZATION OF LTR III-BINDING BIOISOSTERES
CONJUGATED WITH NAPHTHALENE DIIMIDES FOR DUAL HIV-1 INHIBITION**Rotundo G.¹, Cannistrà M.F.S.¹, Rocca R.¹, Doria F.², Gargano A.¹, Xiao W.J.³, Alcaro S.¹¹ *Dipartimento di Scienze della Salute, Università "Magna Græcia" di Catanzaro, Campus Universitario "S. Venuta", Viale Europa, 88100 Catanzaro, Italy*² *Dipartimento di Chimica, Università degli studi di Pavia, V. Torquato Taramelli 10, 27100, Italy*³ *College of Chemistry, Central China Normal University, 152 Luoyu Road, Hongshan District, 430079, China*Giorgia.rotundo003@studenti.unicz.it

Nucleic acids can fold into non-canonical G-quadruplex (G4) structures implicated in crucial genomic processes like replication and transcription. In HIV-1, the etiologic agent of AIDS, these regulatory sequences reside within the U3 promoter region of the long terminal repeats (LTR). Specifically, the LTR III domain comprises three distinct elements—the G-quadruplex core, a junction region, and a stem-loop motif—which cooperatively regulate viral transcription. Consequently, developing selective small molecules to stabilize this architecture represents a key therapeutic strategy to effectively suppress viral replication. [1] Building on previous *in silico* investigations based on the 6H1K structure [1] and subsequent experimental validation from work currently under submission, this study focuses on developing bioisosteric analogues of a ligand that selectively intercalates into the stem-loop. Molecular docking screenings were extended across all ten target conformations, using the binding affinity of the reference compound as a threshold. This approach enabled the selection of candidate molecules exhibiting favorable binding affinities, with binding free energies lower than -7 kcal/mol. Subsequently, a synthetic study was undertaken, leading to the successful preparation of two bioisosteric derivatives, which were isolated by extraction, purified via chromatographic techniques, and structurally confirmed by NMR spectroscopy. To enhance the inhibition of viral replication, this study pursues a novel strategy based on the design of dual-site targeting molecules, it proposes the conjugation of these two bioisosteres to a naphthalene diimide (NDI) core, a scaffold widely validated in the literature as a selective G4 ligand.[2] Through the rational design and chemical synthesis of a suitable linker, this strategy aims to simultaneously and synergistically target the different regions of the LTR III sequence, thereby resulting in a dual inhibitory effect.

Acknowledgements: Italian Ministry of Education - PRIN STRAND 2022BL3L7A.**References:**

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17th Young Medicinal Chemists' Symposium
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P083

**TWO-PRONGED PHENOTYPIC APPROACH TO IDENTIFY NEW AND PROMISING
ANTI-MYCOBACTERIUM ABSCESSUS AGENTS**Dragone C.^a, Poma N.^b, Massari S.^a, Manfroni G.^a, Barreca M.L.^a, Rindi L.^b, Sabatini S.^a^a Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia, via del Liceo 1, I-06123
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Historically, the whole-cell assay has generally outclassed target-based methods as the main approach to discover novel antimicrobial drugs. This is particularly true for antimycobacterial drugs, where the peculiar cellular structure of mycobacteria is responsible for a lack of correspondence between the biochemical and the phenotypic assays.[1] Moreover, phenotypic or cell-based screening can be a rapid method for discovering new antimicrobials, has the advantage of not being biased toward a known target and therefore has the potential to identify new molecular targets.

Nontuberculous mycobacteria (NTM), consisting of all *Mycobacterium* species except for *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*, are a group of approximately 200 ubiquitous environmental species, generally endowed with low pathogenicity to humans.[2] The most relevant NTM species for human diseases are those belonging to *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* (*Mab*).[3] The hydrophobic lipid-rich cell wall constitutes a strong barrier to the penetration of various drugs, representing a major contributor for intrinsic resistance of NTM to many antimicrobial compounds currently available.[4] *Mab* is a rapidly growing mycobacterium associated with several diseases in humans, of which lung disease is the most common, particularly in patients with underlying lung disease such as cystic fibrosis (CF).

Currently, the therapy of *Mab* infections is almost "empiric", involving anti-mycobacterial drugs identified to treat *M. tuberculosis* infection that is a completely different microorganism for its structure, biochemical patterns, mode of growth and physio-pathogenicity. To date, no drugs completely designed to be active against *Mab* infections have been reported. Research about anti-*Mab* drugs is still in its infancy due to the poor knowledge about this emerging pathogen. Treatment of *Mab* requires 18 months of multidrug therapy which includes macrolide-based combination therapy with two parenteral agents for the initial phase. [4] High rates of antimicrobial resistance are seen in *Mab*, and patients experience multiple relapses with low cure rates. Given the current poor outcome in patients with *Mab* infection and the lack of a sufficient pipeline of new drug candidates,[5] more effective antimicrobials are needed not only for improve the killing efficacy but also to reduce the time of treatment.

Herein we report the results of our project (FFC#10/2024) that aims to contribute to contrast *Mab* spread by a two-pronged strategy involving phenotypic medicinal chemistry approaches. In the first strategy we exploited our in-house library of quinolone antibacterial compounds in search of Hit compounds endowed of anti-*Mab* activity. In the second one will take advantage from High Throughput Screening (HTS) procedures already reported in literature, selecting Hit compounds not yet developed by other medicinal chemistry groups. This project was funded by the Fondazione per la Ricerca sulla Fibrosi Cistica – ETS (www.fibrosicisticaricerca.it), in particular the Alba-Cuneo Delegation, which we would like to acknowledge.

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P084

MICROWAVE-ASSISTED SYNTHESIS OF TUBULIN ASSEMBLY INHIBITORS AS ANTICANCER AGENTS

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The microwave-assisted synthesis of novel pyrrole and indole derivatives was carried out, resulting in substantially shorter reaction times and improved yields. The design of these new tubulin assembly inhibitors was based on the application of both aryl ring reversal and conjunctive approach strategies (Figure 1). Among the synthesized compounds, (4-(4-methoxyphenyl)-1-(pyridin-2-yl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**4**) showed remarkable biological activity, inhibiting [³H] colchicine binding by 78% and suppressing the proliferation of MCF-7 breast cancer cells with an IC₅₀ value of 9.6 nM. Moreover, compound **4** exhibited potent antiproliferative effects against HCT116, BX-PC3, and Jurkat cancer cell lines, with IC₅₀ values of 18, 17, and 41 nM, respectively. It also induced significant morphological alterations in spheroids derived from both BX-PC3 and HCT116 cell lines.

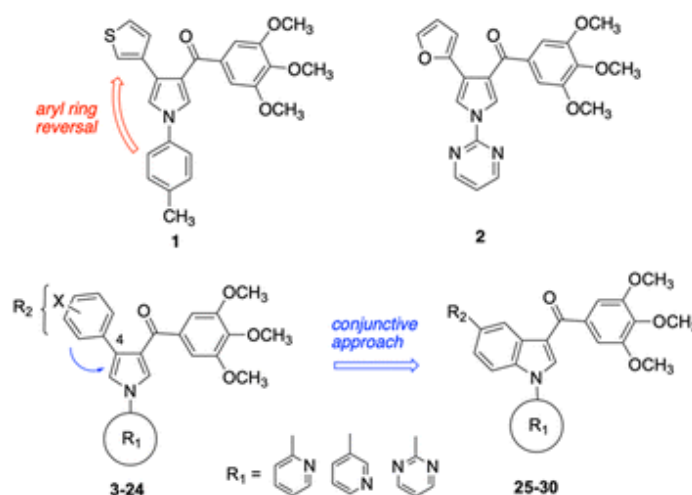


Figure 1. General structures: reference compounds **1** and **2**, new pyrrole **3–24** and indole **25–30** derivatives.

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Messina, Italy - September 13-16, 2026

17th Young Medicinal Chemists' Symposium
Nuove Prospettive in Chimica Farmaceutica

P085

DISCOVERY OF NOVEL INDOLE-BASED DERIVATIVES AS POTENT
SARS-CoV-2 INHIBITORS TARGETING THE SPIKE PROTEINSardo I.^a, Bertamino A.^a, Ostacolo C.^a, Franci G.^b, Campiglia P.^a^aDepartment of Pharmacy, University of Salerno, 84084 Fisciano (SA), Italy^bDepartment of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno,
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The rapid evolution of SARS-CoV-2 variants highlights the need for novel small-molecule targeting key steps of viral entry and replication. In this context, the spike protein represents an attractive target due to its role in mediating binding to the host Angiotensin Converting Enzyme 2 (ACE2). [1] To address this challenge, a focused library of indole-based derivatives was designed based on a previously identified hit (compound 34), guided by structure-activity relationship (SAR) analysis and molecular modeling studies. [2]

Key structural modifications were introduced on the indole core and side chains to explore the SAR and to evaluate the effect of substituents on antiviral potency. The compounds were synthesized via alkylation, Mannich reaction, and reductive amination, allowing systematic modification of the indole scaffold. Cytotoxicity profile was evaluated on VERO-76 cell line using the MTT assay, while antiviral activity was assessed by the analysis of the viral plaque reduction. To support these experimental findings, molecular docking studies were performed on the spike protein binding pocket to rationalise ligand-target affinity and provide insights into the putative binding mode of the most active analogues.

All derivatives displayed an optimal safety profile in the VERO-76 cell line ($CC_{50} > 100 \mu M$), thus confirming their suitability for further evaluation. Among the synthesized analogues, compound **SP2** emerged as the most potent, exhibiting an IC_{50} of $6.65 \mu M$. SAR analysis highlighted the critical role of the ester moiety at position 5 of the indole core. Moreover, the side chain modifications played a key role in determining antiviral potency, suggesting its crucial role in modulating ligand-target affinity. On the other hand, structural modifications with the aim of increasing conformational rigidity or the introduction of highly polar groups led to a loss of activity, indicating that both molecular flexibility and specific physicochemical properties are essential for antiviral efficacy.

Overall, these findings identify novel indole-based small molecules as promising scaffolds for the development of SARS-CoV-2 inhibitors, providing a solid basis for further lead optimization and mechanistic investigations.

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P086

NOVEL *para*-PHENYLENEDIAMINE-BASED DERIVATIVES AS RECEPTOR TYROSINE KINASE-LIKE ORPHAN RECEPTOR 1 (ROR1) INHIBITORS: AN IN VITRO PRELIMINARY CHARACTERIZATION

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ROR1 (Receptor tyrosine kinase like Orphan Receptor 1), reported as an orphan receptor for a long time, has been recently identified as target of Wnt signaling, which is an ancient and highly conserved family of proteins playing a pivotal role in embryonic development and adult tissue homeostasis [1]. The increased attraction in the pseudo-kinase functionality, besides of its pro-survival mechanisms in multiple cancer cell lines, can be further explained by its peculiar expressional behavior: ROR1 is an embryonic protein, missing in most tissues during adult life, while it results highly expressed in several tumor types, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), large B-cell lymphoma (DLBCL) [2]. This property, together with the scarce number of molecules effective against ROR1, led us to design and develop a research program aimed to the discovery of new chemical entities able to inhibit ROR1 thus interfering with its pro-tumoral activity [3]. Step-by-step *in silico* studies guided the design and synthesis of *para*-phenylenediamine-based compounds. SPR and CETSA analyses, coordinated with cytotoxicity assays carried out on JeKo-1 (mantle cell lymphoma) and SH-SY5Y (neuroblastoma cell) cell lines overexpressing ROR1, demonstrated the strong affinity and the anticancer potential of the synthesized molecules, respectively, further confirming its mechanism of action. Moreover, pharmacokinetic assessment revealed a good stability profile for these molecules, paving the way for additional SAR studies and for the development of new ROR1 inhibitors. These findings contribute to the biochemical understanding of ROR1 signaling in tumor progression and highlight the potential of this target for therapeutic intervention in oncology.

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P087

PHENOTYPE-GUIDED TARGETING OF THE ADENOSINE AXIS: SUBTYPE-SPECIFIC TUMOR CONTEXT MODULATORS FROM 3D MODELS

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The development of universal anticancer therapies remains challenging due to the pronounced biological heterogeneity of tumors and the complexity of tumor microenvironments. Many solid tumors display dysregulated adenosinergic signaling accompanied by subtype-specific changes in adenosine receptor (AR) expression and elevated extracellular adenosine generated by hypoxia-driven ATP metabolism [1]. These features promote tumor proliferation, migration, and resistance to therapy, suggesting that AR ligands should be considered tumor-context modulators rather than classical cytotoxic agents.

This study applies a phenotype-guided strategy to investigate subtype-selective AR ligands across glioblastoma (1321N1, LN229, SNB-19 and primary glioblastoma cells), colorectal (Caco-2, HCT116), and prostate (DU145, LNCaP, PC3) cancer models. The investigated novel nanomolar-affinity ligands were based on distinct chemical scaffolds: *4-phenylpyridine-3,5-dicarbonitriles* as A₁AR agonists, *adenine*-derived scaffolds as A_{2A}AR antagonists, and *adenosine*-derived scaffolds as A₃AR agonists. Drug responses were evaluated in both 2D monolayers and 3D tumor spheroids to better reproduce *in vivo*-like resistance. A multiparametric platform combined 2D and 3D viability assays, time-lapse imaging, spheroid morphological integrity analysis, cell-cycle profiling, apoptosis/necrosis assays, scratch migration assays, and cAMP accumulation studies to characterize receptor signaling and distinguish agonism from inverse agonism.

Subtype-specific activity revealed clear tumor-dependent vulnerabilities that correlated with differences in receptor expression levels. A₁AR agonists showed pronounced anti-glioblastoma activity consistent with the functional relevance of A₁AR-mediated signaling in these models. In colorectal tumor models, A_{2A}AR antagonists demonstrated stronger pro-apoptotic effects than inverse agonists despite comparable receptor affinity, indicating that downstream signaling efficacy rather than binding alone determined functional outcomes, a phenomenon also observed in neurodegenerative diseases [2]. A_{2A}AR antagonists inhibited astrocytoma and colorectal tumor cells through anti-proliferative and anti-migratory effects that remained evident in 3D spheroids [3]. A₃AR agonists were most effective in prostate cancer models, where they disrupted spheroid integrity and reduced invasive behavior. Importantly, activity against prostate tumor spheroids was driven more strongly by compound lipophilicity and penetration into the 3D structure than by differences in receptor affinity, highlighting the importance of physicochemical properties for drug efficacy in complex tumor models.

Overall, the findings emphasize that adenosine receptor modulation represents a context-dependent immunometabolic strategy in which therapeutic efficacy is determined by receptor subtype, tumor phenotype, and microenvironmental conditions, providing a rationale for personalized purinergic cancer therapies.

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P088

ISOCYANIDES: AN UNCONVENTIONAL FUNCTIONAL GROUP AS A HEME-COORDINATING MOTIF FOR IDO1 INHIBITION

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Isocyanides represent a unique and underexplored functional group in medicinal chemistry, characterized by a divalent carbon atom bearing a lone pair and ambivalent electronic character. While traditionally employed in multicomponent reactions (e.g., Ugi chemistry),¹ their strong σ -donor and weak-to-moderate π -acceptor properties enable coordination to transition metals, including heme iron centers.^{2,3} Despite these features, their application as pharmacophore moieties remains limited; however, emerging evidence highlights their potential as unconventional metal-binding motifs.³

Here, we investigated isocyanides as novel heme-coordinating groups for the development of holo-inhibitors of indoleamine 2,3-dioxygenase 1 (IDO1), a heme-containing enzyme involved in tryptophan catabolism and frequently overexpressed in cancer. Starting from epacadostat (Figure 1),⁴ a class II *holo*-IDO1 inhibitor, a first series of vinyl isocyanides was designed through a molecular simplification approach, by replacing the oxadiazole core with a phenyl ring and introducing halogen substituents (Cl, F, Br) to modulate electronic and steric properties. The compounds were synthesized via a multistep procedure involving a condensation reaction followed by dehydration.

Biological evaluation showed that all compounds induced a red shift of the IDO1 Soret band from ~404 nm to ~424 nm in the 1–10 μ M range, indicating direct coordination to the heme iron. Notably, *p*-fluoro and *p*-chloro derivatives exhibited a pronounced shift already at 1 μ M, suggesting preferential interaction with the ferrous (Fe^{2+}) state. These observations were supported by enzymatic inhibition data, with IC_{50} values of 876 nM and 595 nM, respectively. The *p*-fluoro disubstituted compound retained submicromolar activity in A375 cells (IC_{50} = 952 nM) and showed no detectable cytotoxicity up to 10 μ M.

To address the metabolic instability associated with the methyl ester moiety, a second-generation library was designed by introducing more stable and decorated amide side chains. Finally, additional isocyanoacetamides were synthesized by multicomponent chemistry (third series).⁵ All the synthesized compounds are undergoing further evaluation, including in vitro metabolic profiling and computational studies to investigate the NC-Fe^{2+} coordination.

Overall, this study provides an initial proof of concept that isocyanides can effectively target the heme iron of IDO1, highlighting their potential as unconventional metal-binding pharmacophores. At the same time, the project remains open-ended, with further optimization and exploration of second- and third-generation compounds currently in progress.

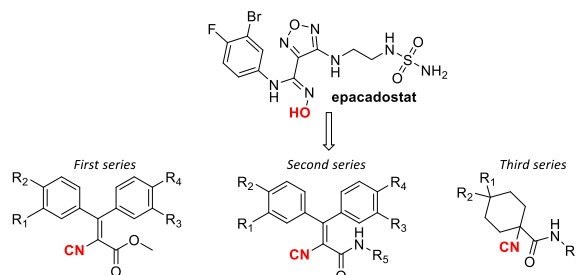


Figure 1. Structures of epacadostat and isocyanides synthesized

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P089

TARGETING TLR-MEDIATED INFLAMMATION IN METABOLIC AND SYSTEMIC DISEASE

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Inflammation is a fundamental biological response essential for tissue repair and homeostasis; however, when chronic, it contributes to the development of numerous non-communicable diseases (NCDs), including cardiovascular, neurodegenerative, oncological, and metabolic disorders such as obesity and type 2 diabetes mellitus [1–3]. These conditions share a common background of chronic low-grade inflammation that disrupts metabolic homeostasis and promotes insulin resistance, underlying the concept of “diabesity.” Adipose tissue plays a central role in this process by acting as an endocrine and immune organ that releases pro-inflammatory mediators, thereby sustaining a vicious cycle between inflammation and metabolic dysfunction.

Given the central role of inflammation across NCDs, targeting key inflammatory pathways represents a promising therapeutic strategy. Toll-Like Receptors (TLRs), particularly TLR2 and TLR4, are critical mediators linking metabolic stress to innate immune activation [4,5]. Modulation of signal transduction following TLR activation offers a valuable opportunity for the development of novel therapies for inflammation-driven diseases.

Based on this rationale, a series of small-molecule modulators targeting TLR2/4 activation were designed, synthesized, and screened to identify dual inhibitors. Screening in HEK293 reporter cells overexpressing TLR2 or TLR4 identified several compounds that significantly inhibited NF- κ B signaling without affecting cell viability or showing agonistic activity. Lead compounds exhibited concentration-dependent inhibition in the low micromolar range for both receptors. These effects were confirmed in THP-1 macrophages and primary human peripheral blood mononuclear cells, where the compounds reduced TLR2- and TLR4-mediated tumor necrosis factor secretion while preserving cell viability. These findings highlight promising candidates for further therapeutic development.

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P090

DEVELOPMENT OF NOVEL ORTHOSTERIC NS2B/NS3 PROTEASE INHIBITORS

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Flaviviruses, including Dengue virus (DENV), Zika virus (ZIKV), and West Nile virus (WNV), continue to represent a major global public health concern due to their widespread distribution, increasing incidence, and the lack of broadly effective antiviral therapies. Among the viral proteins, NS2B/NS3 [1], the main serine protease, plays an essential role in viral polyprotein processing and replication, making it an attractive target for the development of direct acting antivirals. The preferred natural cleavage sequence of Zika virus NS2B/NS3, for example, constitutes a multibasic amino acids pattern with predominantly arginine in the P1 position, and one or two more basic residues in P2- and P3 positions. Accordingly, di- or tribasic P3-P1 segments are a common motif in the majority of peptidic and peptidomimetic flavivirin inhibitors [2,3]. In this work, we envisaged the development of novel NS2B/NS3 protease inhibitors (Figure 1) based on arginine mimetic moieties [4,5]. The first series of radially symmetric bisbenzamidine derivatives (**2-4**) was synthesized starting from triphenyl methanetricarboxylate (**1**). The second approach focused on diketopiperazine (**6**) and macrocyclic (**7**) compounds, both were accessible from Boc-4-cyano-L-phenylalanine (**5**). The synthesized compounds will be evaluated against the NS2B/NS3 proteases of DENV, ZIKV, and WNV to determine their inhibitory activity and to assess their potential as broad-spectrum antiviral agents.

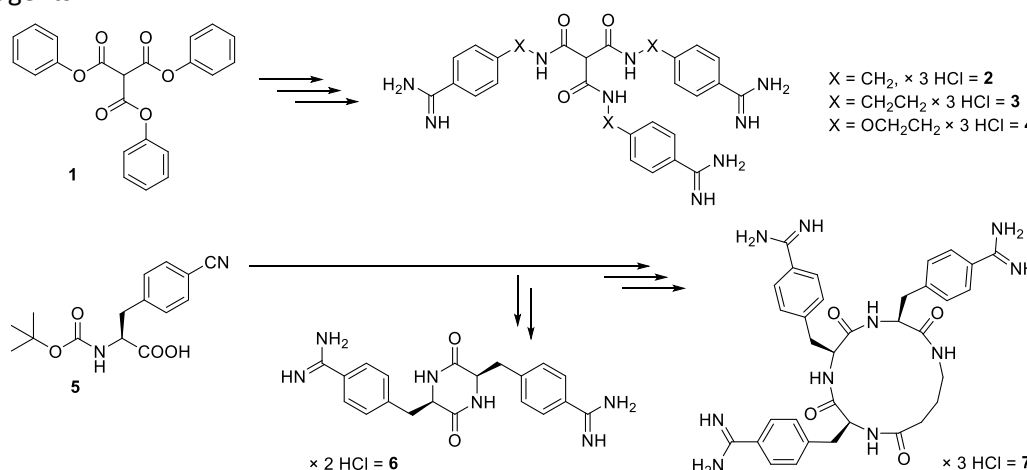


Figure 1. Peptidomimetic benzamidine derivatives.

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P091

DEVELOPMENT OF NOVEL ALLOSTERIC GLUTAMINASE 1 INHIBITORS AS ANTICANCER AGENTS

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In recent years, glutamine metabolism has emerged as a major focus in cancer research. Many tumor cells rely on this amino acid as a key energy source, leading to a condition known as “glutamine addiction” [1]. Glutaminase 1 (GLS1) is the rate-limiting enzyme of glutaminolysis and therefore represents an attractive target for the development of antiproliferative agents. Two main classes of GLS1 inhibitors have been developed: active-site inhibitors, such as 6-diazo-5-oxo-L-norleucine (DON), whose use was limited by off-target toxicity, and allosteric inhibitors, including BPTES, which offered higher selectivity and safety [2]. BPTES binds to the activation loop of GLS1, stabilizing the enzyme in an inactive conformation. Although it showed good antiproliferative activity *in vivo*, its poor aqueous solubility, limited metabolic stability, and low bioavailability have hindered its clinical application. To address these limitations, several BPTES analogues have been designed. However, only two compounds (*i.e.*: **CB-839** and **IPN60090**) have advanced to clinical trials, underscoring the need for further optimization of GLS1-targeted therapies [3].

This project involves the chemical synthesis of novel allosteric GLS1 inhibitors of type **1**, characterized by a *N*-(4-([1,1'-biphenyl]-4-carbonyl)phenyl)carboxamide scaffold (**Figure 1**), which are structurally different from BPTES analogues. The new compounds were identified by a fragment-based drug design approach applied to an AIFA drug bank. The best candidates were ranked through docking and molecular dynamics studies. This strategy will enable a more comprehensive exploration of GLS1 allosteric binding landscape and the rational optimization of the newly identified scaffold. The obtained results will be discussed.

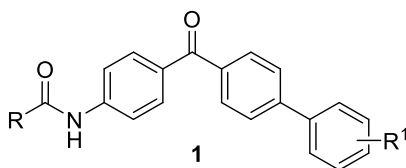


Figure 1. General structure of novel allosteric GLS1 inhibitors.

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P092

**DISCOVERY OF NOVEL SALICYLATE SYNTHASE INHIBITORS AS ANTI-VIRULENCE AGENTS
AGAINST MYCOBACTERIUM ABSCESSUS**

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Mycobacterium abscessus (Mab) is an emerging non-tuberculous mycobacterial pathogen associated with severe pulmonary infections and limited therapeutic options. The increasing incidence of antimicrobial resistance highlights the need for innovative therapeutic strategies [1]. Targeting virulence pathways rather than bacterial viability represents a promising approach to reduce the selective pressure responsible for resistance development [2]. In this context, salicylate synthase (Mab-SaS), the first enzyme involved in siderophore-mediated iron acquisition, has emerged as an attractive anti-virulence target [3,4].

To identify novel Mab-SaS inhibitors, a fragment-based drug discovery campaign was combined with structural biology studies. Fragment screening led to the identification of picolinic acid as a promising binder, and co-crystallization experiments provided the crystal structure of the Mab-SaS–picolinic acid complex at 1.67 Å resolution. [5].

Based on this results, a series of substituted pyridine derivatives was designed and synthesized through a structure-guided medicinal chemistry approach aimed at exploring the influence of substitution patterns on enzyme inhibition. The compounds were characterized and biologically evaluated against Mab-SaS, providing valuable structure–activity relationship information and identifying key molecular features required for productive target engagement.

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P093

METABOLEX: AN INTEGRATED PLATFORM FOR METABOLITES GENERATION AND METABOLIC PATHWAY ANALYSISVittorio S.¹, Lunghini F.², Agazzi G.², Tazzari V.², Fava A.², Macorano A.¹, Vistoli G.¹, Beccari A.R.²¹ *Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Via Luigi Mangiagalli 25, I-20133 Milano, Italy*² *EXSCALATE, Dompé Farmaceutici SpA, Via Tommaso de Amicis 95, 80123 Naples, Italy
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Reliable prediction of drug metabolism is essential for early evaluation of safety liabilities and optimization of pharmacokinetic profiles during drug discovery. [1]

Here, we introduce MetabolEx, an integrated computational platform that combines rule-based metabolite generation with machine-learning-driven prioritization to predict both Phase I and Phase II metabolic transformations. [2]

MetabolEx is built upon 194 manually curated reactions encoded in SMIRKS format and employs classification models trained on a dataset of 41,041 experimentally derived substrate-metabolite pairs aggregated from multiple sources. This hybrid strategy enables extensive generation of chemically plausible metabolites while controlling the combinatorial growth inherent to recursive metabolism prediction through probabilistic filtering.

The platform was evaluated using 219 external compounds across three levels of recursive prediction. For first-generation metabolites (L1), MetabolEx achieved a recall of 0.84. At the second level (L2), it delivered approximately twice the precision of benchmark methods while maintaining a recall of 0.57 and markedly reducing the false positives rate. For third-generation metabolites (L3), the approach yielded a fivefold increase in precision and a 25-fold decrease in false positives compared with exhaustive enumeration, with a recall of 0.35. These findings highlight the effectiveness of probabilistic prioritization in refining large sets of generated metabolites into biologically meaningful predictions.

By covering eight major metabolic reaction families, MetabolEx represents a comprehensive solution for metabolic and toxicological assessment. The platform also offers interactive visualization of metabolic networks and automated toxicity annotations, and is freely accessible at <https://metabolx.exscalate.eu>.

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P094

Nav1.5 N347K REMODELS THE ELECTROSTATIC LANDSCAPE FOR MEXILETINE BINDING: MOLECULAR DYNAMICS INSIGHTS INTO BRUGADA SYNDROME

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The Nav1.5 N347K mutation causes Brugada syndrome by suppressing sodium current in channels correctly trafficked to the plasma membrane. Paradoxically, overnight mexiletine incubation rescues 21% of lost INa in N347K [1], while reducing current by 85% in the adjacent A344S variant — a mutation-selective rescue with no structural explanation. We investigated this mechanism using 500 ns molecular dynamics (MD) simulations of five systems: apoWT, N347K (apoMutant), WT + mexiletine, N347K + neutral mexiletine, and N347K + protonated mexiletine (PDB 8VYK, CHARMM36m, OpenMM). MM-GBSA binding free energy, contact analysis (4.5 Å cutoff, 10,000 frames), ProLIF interaction fingerprinting, and DBSCAN conformational clustering were computed. In simulations using neutral mexiletine — the standard modelling assumption — the drug occupies a P-loop adjacent pocket formed by the N347K substitution. Contact analysis over 10,000 frames shows dominant contacts with PRO348 (88.0%), THR353 (88.8%), ASP349 (74.6%), and PHE355 (49.8%). MM-GBSA binding free energies revealed 6.5-fold selectivity for the mutant channel ($\Delta G = -18.47 \pm 3.81$ kcal/mol) versus wild-type ($\Delta G = -2.84 \pm 5.10$ kcal/mol), driven by shape complementarity ($\Delta\Delta\text{VDWAALS} = -20.51$ kcal/mol). Salt bridge K347–D356 occupancy increases from 39.2% (apoMutant) to 51.2% (holoMutant), suggesting indirect allosteric stabilisation of the P-loop. However, at physiological pH 7.4, mexiletine exists predominantly in its protonated, positively charged form ($+\text{NH}_3$, $\text{pK}_a \approx 9.1$). Simulations with protonated mexiletine reveal a fundamentally different behaviour: the drug leaves the P-loop region within ~50 ns and relocates to the Domain III/IV junction, where it remains for the remainder of the 500 ns trajectory (95.2% of frames). The driving force is electrostatic repulsion between K347⁺ and the protonated amine (+1) of mexiletine. At the new binding site, strong cationic interactions are established with ASP1714 (67.9% hydrophobic, 21.9% cationic, ProLIF) and ASP1423 (65.4% cationic, 39.2% H-bond donor), alongside hydrophobic contacts with VAL1400 (54.9%), ILE1424 (25.5%), and LEU1717 (24.3%). MM-GBSA binding free energy at this site is $\Delta G = -15.01 \pm 5.59$ kcal/mol. Notably, this Domain III/IV region corresponds to the classical high-affinity local anaesthetic receptor site identified for lidocaine and flecainide [2]. Despite mexiletine's relocation, K347–D356 salt bridge occupancy (44.0%) remains above the apoMutant baseline (39.2%), consistent with an allosteric stabilisation mechanism that could contribute to the partial current rescue observed in vitro. Comparison simulations with protonated mexiletine in wild-type Nav1.5 are currently underway to determine whether the Domain III/IV binding is mutation-selective or a general channel property. These results highlight the critical importance of correct protonation state in drug–channel modelling and provide a structural rationale for mutation-specific mexiletine rescue in Nav1.5 N347K.

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P095

MEGA PROTAC RELOADED: A ROUTE TO TERNARY COMPLEX MODELING LEVERAGING KNOWLEDGE-BASED BURIED-SURFACE AREA AND LINKER CONFORMATIONAL FREEDOM DATA

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High-throughput virtual screening of Proteolysis-targeting chimeras (PROTACs) is a challenging and intensive computational task. The complexity of the simulation intrinsically arises from the system to be modeled, including the two proteins involved in the PROTAC MoA, the protein of interest (POI) and a Ubiquitin E3 ligase, and the heterobifunctional PROTAC molecule. [1] Mechanistically, an effective PROTAC should be able to chemically induce the proximity between the POI and the E3 ligase, assembling a ternary complex where the PROTAC is interacting with each protein. Furthermore, new POI:E3 ligase protein-protein interactions (PPIs) are established, contributing to the stabilization of the whole complex. [2] In recent times, several software were released with the aim of accomplishing the ternary complex modeling problem but, despite the extensive research efforts, the development of a highly reliable and fast enough computational tool in producing the desired results is still an open research field. Among them, the computational pipeline MEGA PROTAC is particularly promising due to its ability to reproduce acceptable-quality ternary complex structures without exploiting any refinement techniques or time-consuming molecular dynamic calculations. [3]

Here, we tested and analyzed the performance and the limits of MEGA PROTAC, with the final aim of developing an improved computational pipeline based on a similar workflow. Our efforts were addressed on improving the selection criteria of protein-protein complexes, which, for example, are not taking into account the conformational freedom of specific PROTAC molecules, while prioritizing complexes with higher solvent-accessible surface area. In addition, MEGA PROTAC exploits the rigid binding conformation found in the solved ternary complex crystal structure as input ligand for PROTAC docking, and that rigidity is not applicable in a real-case scenario where the actual PROTAC binding conformation is unknown. MEGA PROTAC Reloaded is the result of our work, aiming to improve the weaknesses of the original computational pipeline and provide a practical tool for real virtual screening of PROTACs (Figure 1).

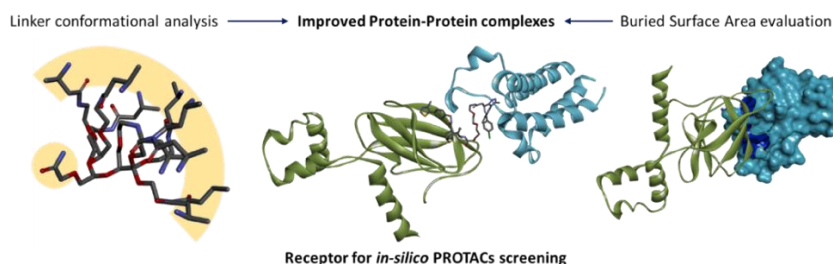


Figure 1

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P096

NOVEL ANTITUSSIVE DERIVATIVES AS POTENTIAL SIGMA RECEPTOR LIGANDS

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Sigma receptors are classified into two subtypes: sigma-1 receptor ($\sigma 1R$) and sigma-2 receptor ($\sigma 2R$). Both subtypes have diverse expression patterns and are widely distributed in the brain and periphery, playing a role in a range of physiologic and pathologic processes [1, 2]. $\sigma 1R$ is a therapeutic target for neurological disorders such as Alzheimer's and Parkinson's diseases, depression, and drug addiction, whereas the $\sigma 2R$ subtype is overexpressed in many cancer cells. In this context, $\sigma 2R$ agonists can be potential anticancer agents or can be used as a target of radio-labelled ligands for the identification of solid malignant tumors. Over the years, the activation of sigma receptors, particularly $\sigma 1R$, has also been linked to the onset of antitussive effects. For example, carbetapentane and butiramate (Fig. 1), are well-known antitussive agents that are also classified as an $\sigma 1R$ -agonist [3]. However, they present a low selectivity towards $\sigma 2R$ subtype. On this basis, we planned to synthesize a small library of molecules (figure 1), **1** and **2** retaining the original structural motifs of carbetapentane and butiramate ligands, varying the intermediate spacer and the amine portion, by replacing the diethylamino group with other known cyclic amine gifted with $\sigma 1R$ and/or $\sigma 2R$ affinity. A total of twenty compounds have been synthesized and *in-silico* evaluated for their potential σR affinity.

We conducted a computational study for both $\sigma 1$ and $\sigma 2$ receptors, which verified that the scaffold of the synthesized compounds appeared to have the appropriate properties to enter and interact with the receptor pocket; naturally, there were variations depending on the type of structure and receptor considered. In certain instances, the molecular volume of basic nitrogen atom and its proximity to the center of gravity of the molecule may be important contributors to the lower affinity. The nitrogen is nearly at the center of the pharmacophore models found, but it is usually pushed toward one of the two hydrophobic nuclei.

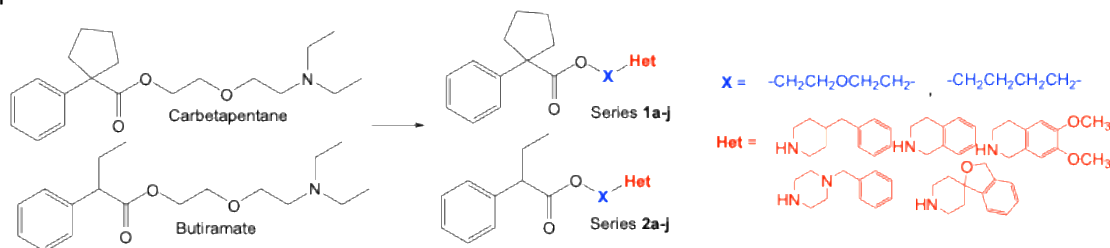


Figure 1. Novel compounds (**1a-j** and **2a-j**), derived from known antitussive agents synthesized from our group.

The compounds are currently being evaluated for their displacement percentage towards SRs, at 50 nM of concentration, and the best candidates will be tested for the evaluation of K_i 's and cytotoxic studies.

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- [1] Malar, D.S., *et al.* *CNS Drugs*. 2023, 37, 399—440. [2] Schmidt HR, Kruse AC. *Trends Pharmacol. Sci.* 2019, 40, 636—654. [3] Calderon, S.N. *et al.* *J. Med. Chem* **1994**, 37, 2285 – 2291.

P097

DEVELOPMENT OF NITROGEN-BASED COMPOUNDS AS ANTIVIRAL AGENTS AGAINST FLAVIVIRUSES

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RNA viruses include numerous human pathogens responsible for recurrent outbreaks and represent an ongoing global health threat. The COVID-19 pandemic further highlighted the limitations in responding to emerging viral infections and the urgent need for effective antiviral therapies. Among them, the Flaviviridae family includes the genus *Flavivirus*, comprising major arthropod-borne viruses such as Dengue, Zika, West Nile, Yellow Fever, and Japanese Encephalitis. [1] These viruses are mainly endemic to tropical and subtropical regions, but climate change and global mobility are driving their geographic expansion. *Flavivirus* infections are associated with significant epidemics, including Dengue, while the 2015–2016 Zika outbreak highlighted their pandemic potential. Consequently, Dengue and Zika are prioritized by the WHO among major global health threats, and increasing West Nile virus cases have been reported in Europe, including Italy. [2]

Despite their relevance, no approved antiviral treatments are currently available for flavivirus infections, and therapy remains limited to supportive care. This underscores the urgent need for new antiviral strategies, including broad-spectrum agents active against multiple flaviviruses. [3]

In this context, the project aims to identify and develop novel small-molecule antivirals targeting key viral processes. A random screening of an in-house compound library in ZIKV-infected Vero cells led to the identification of nitrogen-based hit compounds with low micromolar activity and promising selectivity, currently under evaluation against other flaviviruses.

Starting from these results, structural analogues have been designed and synthesized to explore structure–activity relationships and optimize antiviral activity. These compounds are under biological evaluation for antiviral potency, cytotoxicity, and selectivity index. Overall, this scaffold represents a promising starting point for the development of novel antivirals against Zika virus and related flaviviruses.

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P098

MOLECULAR STRIPTEASE OF A THIADIAZOLOPYRIMIDINE HIT YIELDS A STREAMLINED, ARTEFACT-FREE NADPH MIMIC FOR NOX INHIBITION

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The convergence of oxidative stress and inflammation drives neurodegeneration and cancer, positioning NADPH oxidases (NOXs) as critical therapeutic targets [1-3]. Starting from the polyfunctional thiadiazolopyrimidine hit **1** [4], we systematically truncated its peripheral arms to map minimum pharmacophoric requirements. While extensive clipping compromised activity, strategic optimization yielded the streamlined analogue **5** (Figure 1). *In silico*, **5** acted as a competitive NADPH mimic; in cell-free assays, it maintained multi-isoform potency, inhibiting NOX1 and NOX5 at low-micromolar concentrations. In rat brain subcellular fractions, **1** and **5** demonstrated concentration-dependent neuroprotective and antioxidant efficacy (1-10 μ M) by suppressing lipid peroxidation and preserving mitochondrial and synaptosomal viability (Figure 1). Notably, chemical profiling proved that **5** successfully stripped away the pro-oxidant liabilities and radical-scavenging artifacts inherent to **1** (Figure 1). In cancer, **1** displayed some antiproliferative activity, mainly in hematological malignancies. Compound **5**, although aqueous solubility issues limited its cellular antiproliferative performance, represents a specific, artifact-free architectural starting point for future selective NOX inhibitor development.

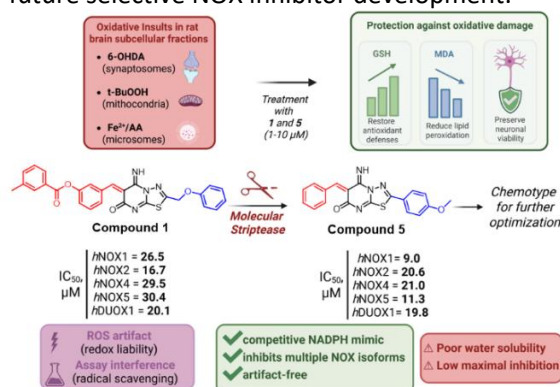


Figure 1. Rational scaffold simplification yields a streamlined, artifact-free NOX inhibitor.

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P099

SIMPLIFICATION AND DERIVATIZATION OF QUINOLINE-CONTAINING M41 LEAD TO THE DISCOVERY OF NADPH OXIDASE ISOFORM-SELECTIVE INHIBITORS EFFECTIVE IN CANCER CELLS

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NADPH oxidases (NOXs) are major sources of reactive oxygen species and attractive therapeutic targets, although the development of isoform-selective inhibitors remains challenging because of the high conservation of their catalytic domains [1]. Starting from the noncovalent inhibitor **M41** [2] and its simplified analog **MC4876**, we designed and synthesized a focused series of quinoline-based derivatives to investigate the structural determinants of NOX selectivity. Structure–activity relationship studies revealed that modifications at the quinoline C2 position and the amine-containing moiety strongly influenced potency and isoform preference. Boc-protected analogs preferentially targeted NOX5, with compound **1a** displaying selective inhibition ($IC_{50} = 1.6 \mu M$), whereas deprotected derivatives generally favored NOX2 inhibition. Replacement of the piperidine ring with tetrahydropyran afforded **MC4953**, a selective NOX1 inhibitor ($IC_{50} = 3.4 \mu M$). Unexpectedly, the bisquinoline derivative **MC4921** emerged as the most potent and selective NOX2 inhibitor identified ($IC_{50} = 1.4 \mu M$; cellular $EC_{50} = 0.89 \mu M$), with target engagement confirmed in both cell-free and cellular assays. Computational studies support binding within the NADPH-binding site and explain the enhanced potency of **MC4921** through additional interactions involved in cofactor recognition. In cancer models, **MC4876** displayed antiproliferative activity, reducing glioblastoma cell viability, glucose uptake, HK2 expression, and mesenchymal markers, while decreasing ROS production and inducing mitochondrial dysfunction and DNA damage signaling in U937 cells. Collectively, these findings identify quinoline derivatives as tunable scaffolds for isoform-selective NOX inhibition and establish **MC4953** and **MC4921** as promising NOX1- and NOX2-selective leads.

References:

[1] Cipriano, A. et al. *J. Med. Chem.* **2023**, 66, 11632-11655. [2] Reis, J. et al. *Nat. Chem. Biol.* **2023**, 19, 1540-1550.

P100

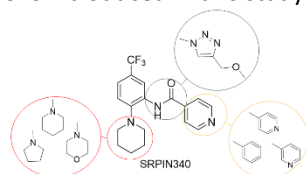
DEVELOPMENT OF NOVEL SRPIN340-INSPIRED 1,2,3-TRIAZOLE DERIVATIVES: SYNTHESIS, CHARACTERIZATION AND ANTITUMOR EVALUATION

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Introduction. Amides constitute a class of compounds widely explored in medicinal chemistry, standing out for their stability, versatility, and biological relevance.¹ Among them, SRPIN340 (Figure 01) has attracted considerable attention as an ATP-competitive inhibitor with high selectivity toward serine/arginine-rich protein kinases (SRPKs), particularly SRPK1 and SRPK2.^{2,3} Considering also the broad pharmacological potential of the 1,2,3-triazole scaffold,³ this study aimed to develop SRPIN340-inspired compounds containing this heterocyclic moiety and to evaluate these derivatives against several tumor cell lines.

Figure 01. Structure of SRPIN340 and the modifications introduced in this study.



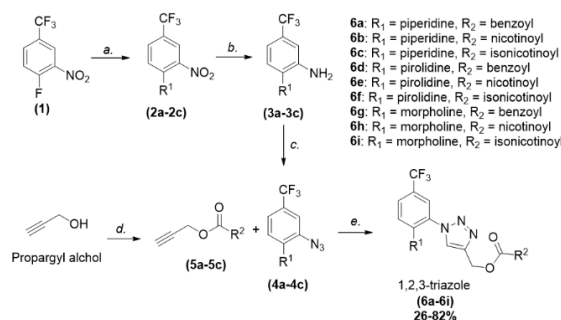
Results and Discussion. The SRPIN340-inspired compounds were synthesized through nucleophilic aromatic substitution, reduction using SnCl₂/HCl, amidation, diazotization, and copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC)³ (Figure 02). The compounds were obtained with yields ranging in 26-82%. After purification by silica gel column chromatography and characterization by LC-MS, infrared (IR) spectroscopy, and ¹H and ¹³C NMR spectroscopy, the derivatives were evaluated for their in vitro cytotoxic activity using the MTT assay against the HepG2 (hepatocellular carcinoma), A375 (melanoma), PC3 (prostate cancer), and U87 (glioblastoma) cell lines, with PNT2 cells used as a non-tumoral control. The IC₅₀ values and selectivity indices (SI) obtained after 48 h of treatment are presented in Table 01.

Table 01. (IC₅₀) and IS values (μmol L⁻¹) for compounds evaluated against tumor cell lines

Compound	PNT2	HEPG2	IS	A375	IS	PC3	IS	U87	IS
SRPIN340	> 160	> 160	NS	105,7	1,51	> 160	NS	73,85	2,16
6a	> 160	72,71	> 2,21	> 160	NS	137,6	> 1,16	104,2	> 1,53
6b	> 160	111,6	> 1,43	> 160	NS	> 160	NS	41,56	> 3,85
6c	> 160	94,19	> 1,69	152,7	> 1,04	> 160	NS	> 160	NS
6d	> 160	122,7	> 1,30	> 160	NS	> 160	NS	> 160	NS
6e	> 160	114,9	> 1,39	> 160	NS	123,3	> 1,29	> 160	NS
6f	> 160	137,8	> 1,16	> 160	NS	144,8	> 1,10	> 160	NS
6g	> 160	129,8	> 1,23	127,1	> 1,25	125,3	> 1,27	141,6	> 1,12
6h	> 160	> 160	NS	> 160	NS	> 160	NS	> 160	NS
6i	> 160	> 160	NS	> 160	NS	> 160	NS	> 160	NS

N.S. No Selective
I.S. Selectivity index

Figure 02. Synthetic methodology for the compounds



Reaction conditions: a) DMF, R¹-NH₂, 60 °C; b) nitrocompound 2a-2c SnCl₂, HCl (conc.), MeOH, reflux 60 °C; c) amine 3a-3c, HCl (4molL⁻¹), NaNO₂, NaH₂PO₄, d) alcohol, acyl halide, Et₃N, CHCl₃, reflux 60 °C e) azide 4a-4c, alkyne 5a-5c, CuSO₄, Sodium Ascorbate, EtOH:H₂O:Dichloromethane, reflux 60 °C.

Conclusions. A series of nine SRPIN340-inspired compounds was synthesized and characterized. Compound 6b showed particularly promising activity against the U87 (glioblastoma) cell line, with an IC₅₀ value of 41.56 μmol L⁻¹ and a selectivity index (SI) > 3.85. These results highlight the potential of triazole derivatives as promising agents against glioblastoma.

Acknowledgments. FAPES, FAPEMIG, CNPq, and CAPES for financial support.

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[1] Kumari, S.; *et al. J. Med. Chem.* 2020, 63, 12290. [2] Siqueira, R. P.; *et al. Eur. J. Med. Chem.* 2017, 134, 97. [3] Sousa, S. M. R.; *et al. Quim. Nova* 2021, 44, 1268.

P101

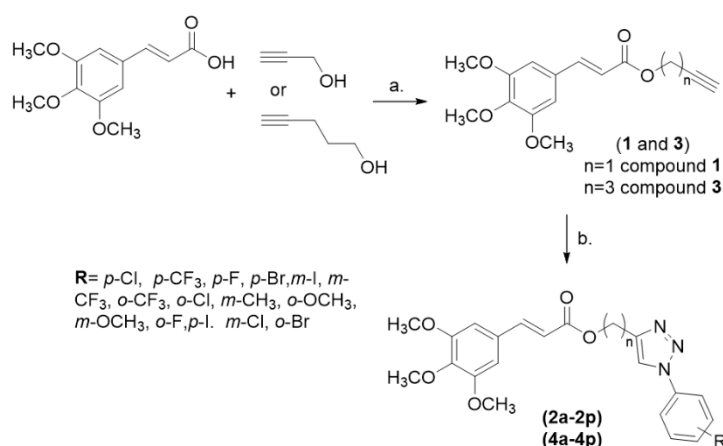
SYNTHESIS AND EVALUATION OF THE ANTIMELANOMA ACTIVITY OF 3,4,5-TRIMETHOXYCINNAMIC ACID-BASED 1,2,3-TRIAZOLE DERIVATIVES

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Introduction. Melanoma is the most aggressive form of skin cancer and accounts for most skin cancer-related deaths. Its high metastatic potential makes the treatment of advanced cases challenging, despite advances in targeted therapies and immunotherapy.^{1,2} In this context, 3,4,5-trimethoxycinnamic acid, a natural cinnamic acid derivative found in *Polygala tenuifolia*, has attracted attention due to its biological activities, including antitumor effects.³ Moreover, the 1,2,3-triazole moiety is associated with several pharmacological properties, particularly anticancer activity.⁴ Therefore, this study aimed to synthesize 1,2,3-triazole derivatives of 3,4,5-trimethoxycinnamic acid.

Figure 01. Synthetic methodology for the compounds introduced in this study



Reaction conditions: a. DIC/DMAP, DCM r.t. b. Ar-N₃ and non aromatic azides, alkyne 1 and 3, CuSO₄·5H₂O, Sodium Ascorbate, EtOH:H₂O:Dichloromethano, r.t. or 70 °C.

of 36.75 μmol L⁻¹ and SI > 4.35 (Table 01).

Table 01. (IC₅₀) and IS values (μmol L⁻¹) for compounds evaluated against tumor cells.

Compound	R	PNT2	A375	IS
4e	<i>m</i> -OCH ₃	> 160	51.16	> 3.12
4l	<i>o</i> -Br	> 160	36.75	> 4.35
4m	<i>p</i> -I	> 160	84.77	> 1.88
4o	<i>p</i> -Br	> 160	73.84	> 2.16

IS: Selective Index

Results and Discussion. A two-step synthetic route involving Steglich esterification and click reactions was used to obtain 32 compounds derivatives (1, 2a–2p, 3 and 4a–4p), with yields ranging from 39% to 96%. After purification and characterization, the synthesized compounds were evaluated for their cytotoxic activity against the A375 tumor cell line (melanoma), with PNT2 non-tumoral cells used as a control. The results identified eight derivatives with higher cytotoxic activity, exhibiting selectivity indices ranging from > 1.11 to > 4.35 and IC₅₀ values ranging from 131.1 to 36.75 μmol L⁻¹. Among these eight derivatives, compounds 4e, 4l, 4m, and 4o exhibiting IC₅₀ values below 100 μmol L⁻¹ and selectivity indices (SI) greater than 2. Compound 4l was particularly noteworthy, with an IC₅₀ value

Conclusions. The results identified triazole derivative 4l as the most promising compound, exhibiting the highest cytotoxic activity and selectivity against the A375 cell line. Therefore, this compound may represent a promising starting point for the development of novel chemotherapeutic agents for melanoma treatment. **Acknowledgments.** FAPES, FAPEMIG, CNPq, and CAPES for financial support.

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[1] Hsieh, M. *et al. Cancer Cell Int.* **2024**, 24, 63. [2] Caraviello, C. *et al., Cancers* **2025**, 17, 2920. [3] Ruwizhi, N. *Int. J. Mol. Sci.* **2020**, 21, 5712. [4] Vaishnani, M. J. *et al. Green Chem. Lett. Rev.* **2024**, 17, 2307559.



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P102

COMPUTATIONAL DRUG REPURPOSING THROUGH HOMOLGY MODELING OF MUTATED VARIANTS OF LANOSTEROL 14 α -DEMETHYLASE

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Candida albicans is an opportunistic fungal pathogen responsible for infections associated with high morbidity and mortality, particularly in immunocompromised patients who develop invasive candidiasis. Mutations in lanosterol 14 α -demethylase (Erg11), the enzyme encoded by the Erg11 gene and the primary target of azole antifungal drugs, can contribute to the development of resistance and reduce the effectiveness of currently available therapies. This study aims to identify potential repurposable drugs capable of interacting with different mutated variants of Erg11. Based on mutations reported in the literature [1], the corresponding mutant amino acid sequences were generated and subsequently used to build three-dimensional protein models through homology modeling using Schrödinger Prime [4]. Molecular docking studies were then performed on these models using libraries of drugs already approved for other therapeutic indications, in order to predict binding affinity. The binding mechanisms investigated included coordination of a nitrogen atom with the heme iron and steric hindrance within the enzyme access channel (SEC) [2, 3]. The integration of these parameters enabled the identification and comparison of compounds displaying favorable binding profiles across the different Erg11 variants. This approach integrates information on resistance-associated mutations, modeling, and virtual screening to identify potential candidates for repurposing as antifungal agents against *C. albicans*, including compounds that may retain activity against Erg11 variants associated with azole resistance.

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- [1] Flowers, S.A. et al. *Antimicrob. Agents Chemother.* **2015**, *1*, 450-460. [2] González-Chávez, R. et al. *Chem. Pharm. Bull.* **2014**, *1*, 16-24. [3] Monk, B. C. et al. *Biochim. Biophys. Acta Proteins Proteom.* **2020**, *3*. [4] Prakash, S. M. U. et al. *Mol. Biol. Res. Commun.* **2020**, *4*, 155-167