

Science Festival with European Researchers' Night, 25.09.2026



Book of abstract

Celebrating Young Researcher Innovators within COST Action CA21111 OneHealthDrugs during the European Researchers' Night: Scientific Dissemination, Science Communication, Public Engagement and Team Building

An inspiring hybrid event bringing together the Young Researcher Innovators (YRIs) of COST Action CA21111 OneHealthDrugs to celebrate scientific excellence. This will foster collaboration, and engage with society during the European Researchers' Night. The event has combined scientific dissemination, science communication, public engagement, and team building, providing an outstanding opportunity to present research, exchange ideas, and develop new collaborations across disciplines and countries.

A joint session with the PhD Programme in Drug Discovery and Development of the Department of Pharmacy and Biotechnology (FaBiT), University of Bologna, entitled "Chemistry for a Better Life and a Better Future", featuring two distinguished guest speakers, Prof. Kelly Chibale and Prof. Gianluca Maria Farinola.

As part of this initiative, parallel outreach activities also took place in partner institutions, creating a shared OneHealthDrugs celebration across multiple institutions. Through the hybrid format, OHD participants from different countries were connected live, allowing them to give pitches and showcase their local European Researchers'; Night activities, while interacting with colleagues throughout the COST network.

Development of Pomegranate-inspired products with anti-infective potential

Lorenzo Raffellini,^a Oliver Keminer,^b Reagon Karki,^b Sheraz Gul,^b Clementina Manera,^a Simona Rapposelli^a

^a University of Pisa, Department of Pharmacy, Italy;

^b Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Hamburg, Germany.

lorenzo.raffellini@phd.unipi.it

Ellagic Acid (EA) represents a polyphenolic compound found in different food sources, such as pomegranate. Among the several biological activities proved by EA, it demonstrated antioxidant, anti-inflammatory and anti-infective effects^{1,2}. In light of the above, our work focused on the extraction of discarded pomegranate peels through eco-friendly procedures to obtain a sustainable EA-rich extract with different potential applications as dietary supplement or personal care product. We preliminary investigated the ecotoxicity of the extract, while antiparasitic studies are currently ongoing. On the other hand, we addressed the topic also from a medicinal chemistry perspective. Specifically, we designed and synthesized a small library of small molecules inspired by urolithins, which are EA metabolites produced by gut microbiota. Among them, urolithin A proved a higher bioavailability than EA and to maintain a comparable biological profile³. Therefore, a part of this project aimed to develop novel anti-infective compounds characterized by a urolithin scaffold. The new urolithin derivatives were investigated for their early ADME-Tox properties with the aim of selecting the most promising to be assessed for their antiparasitic ability.

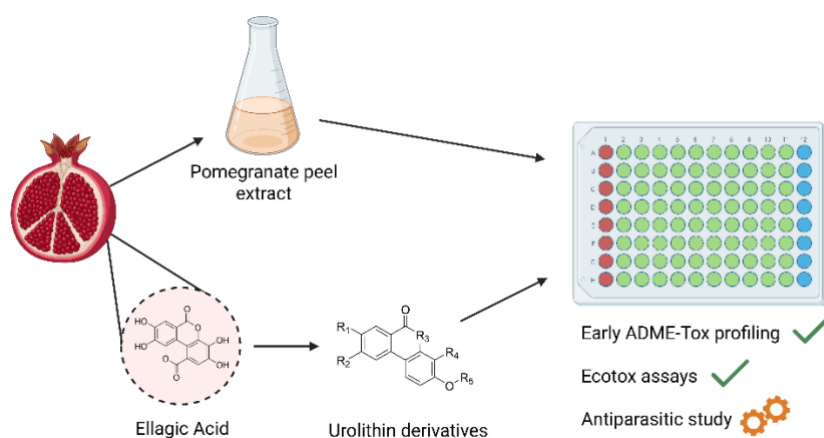


Figure 1 – Schematic visualization of the project workflow.

REFERENCES

- [1] Dell'Agli, M. *et al.* Antiplasmodial activity of Punica granatum L. fruit rind. *Journal of Ethnopharmacology* **125**, 279–285 (2009).
- [2] Acquadro, S. *et al.* Punica granatum Leaf Ethanolic Extract and Ellagic Acid as Inhibitors of Zika Virus Infection. *Planta Med* **86**, 1363–1374 (2020).
- [3] Tomás-Barberán, F. A., García-Villalba, R., González-Sarrías, A., Selma, M. V. & Espín, J. C. Ellagic Acid Metabolism by Human Gut Microbiota: Consistent Observation of Three Urolithin Phenotypes in Intervention Trials, Independent of Food Source, Age, and Health Status. *J. Agric. Food Chem.* **62**, 6535–6538 (2014).

Synthesis and Antileishmanial Evaluation of Chalcone-Based Compounds

Kübra İren,^a Sandra Gemma^b

^aGebze Technical University, Department Of Chemistry, Gebze, Türkiye, ^bUniversity of Siena, Department of Biotechnology, Chemistry and Pharmacy, Siena, Italy
k.iren2023@gtu.edu.tr

Leishmaniasis is a parasitic disease that represents an important public health concern, particularly in tropical and subtropical regions. The limitations associated with current treatment options highlight the need for the development of new antileishmanial compounds. Chalcone-based compounds have attracted attention in antileishmanial drug research due to their structural diversity and reported biological activities [1–3]. In this study, the antileishmanial properties of chalcone-based compounds with potential biological activity will be investigated. Within this scope, selected compounds have been synthesized, and their structural characteristics have been confirmed using appropriate analytical techniques. The activities of the synthesized compounds against *Leishmania* parasites will be evaluated to assess the potential of chalcone-based structures as antileishmanial agents.

Keywords: Chalcones; Antileishmanial Activity; *Leishmania*; Medicinal Chemistry; Bioactive Compounds

REFERENCES

- [1] Pozzetti, L. et al. *Molecules* **2022**, 27, 463.
- [2] Tajuddeen, N. et al. *Int. J. Antimicrob. Agents* **2018**, 51, 311–318.
- [3] de Mello, M. V. P. et al. *Eur. J. Med. Chem.* **2018**, 150, 920–929.

Deep Eutectic Solvent-Mediated Pd-Catalyzed Suzuki–Miyaura Cross-Coupling for the Sustainable Synthesis of New Pyridine Derivatives of Medicinal Interest

Gunel Aliyeva^a, Luciana Cicco^b, Ulviyya Hasanova^a, Vito Capriati^b

^a Baku State University, Baku, Azerbaijan

^b University of Bari “Aldo Moro”, Bari, Italy

E-mail: guneel.aliyeva@gmail.com

This study presents an efficient and environmentally responsible approach to the synthesis of new pyridine derivatives. Suzuki–Miyaura cross-coupling is a valuable method for selectively forming C(sp²)–C(sp²) bonds under mild conditions, with broad functional-group tolerance. It is particularly suitable for constructing heteroaryl–aryl and heteroaryl–heteroaryl frameworks commonly found in biologically active compounds [1]. Pyridine is a versatile heterocyclic scaffold present in numerous pharmaceuticals, including isoniazid, nifedipine, clopidogrel, and lansoprazole. Its diverse substitution patterns make it valuable for developing antibacterial, antihypertensive, anticancer, and other therapeutic agents [2]. Therefore, the synthesis of new pyridine derivatives remains an important research objective.

In this work, brominated pyridine derivatives were functionalized through Pd-catalyzed Suzuki–Miyaura reactions with potassium aryl- and heteroaryltrifluoroborates. The reactions were performed in a deep eutectic solvent composed of choline chloride and glycerol (1:2 molar ratio). This medium offers low volatility, non-flammability, biodegradability, and simple preparation from inexpensive and renewable components.

The reactions were conducted in open air at 80 °C for 6 h using 1 mol% palladium and Na₂CO₃ as the base. The products were purified by column chromatography and characterized by NMR, FT-IR, and mass spectrometry. Following systematic optimization, more than ten substrate combinations were investigated. The protocol showed good efficiency, selectivity, and robustness, affording aryl- and heteroaryl-substituted pyridine derivatives in yields of up to 90%.

In conclusion, this work introduces a practical and more sustainable strategy for preparing pyridine derivatives relevant to medicinal chemistry. By combining palladium-catalyzed Suzuki–Miyaura cross-coupling with a choline chloride/glycerol deep eutectic solvent, the developed approach expands the available synthetic methods for accessing functionalized pyridines while responding to the increasing demand for greener chemical processes.

REFERENCES

- [1] Zhao, Dongbing, Jingsong You, and Changwei Hu. "Recent progress in coupling of two heteroarenes." *Chemistry–A European Journal* 17, no. 20 (2011): 5466–5492.
- [2] Ling, Yong, Zhi-You Hao, Dong Liang, Chun-Lei Zhang, Yan-Fei Liu, and Yan Wang. "The expanding role of pyridine and dihydropyridine scaffolds in drug design." *Drug design, development and therapy* (2021): 4289–4338.

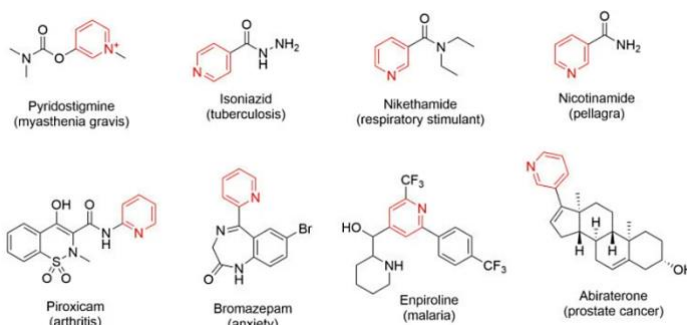


Fig.1 Some commercially available drugs containing the pyridine scaffold.

Targeting the Sulphur Assimilation Pathway in *Pseudomonas aeruginosa*: Discovery of Covalent Inhibitors of Adenosine 5'-Phosphosulfate Reductase Enzyme Activity

Gian Marco Elisi,¹ Matilda Ymeraj,¹ Sarah Hijazi,¹ Rebecca Martedì,¹ Francesco Guggino,² Valeria Buoli Comani,² Carlos A. Ramos-Guzmán,³ Marko Hanževački,³ Adrian Mulholland,³ Marialaura Marchetti,⁴ Barbara Campanini,⁵ Emanuela Frangipani,¹ Giovanni Bottegoni^{1,6}

¹ Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy

² Interdepartmental center Siteia, University of Parma, Parma, Italy

³ Centre for Computational Chemistry, School of Chemistry, University of Bristol, United Kingdom

⁴ Department of Medicine and Surgery, University of Parma, Parma, Italy

⁵ Department of Food and Drug, University of Parma, Parma, Italy

⁶ Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, United Kingdom

Pseudomonas aeruginosa is a daunting ESKAPE pathogen, particularly dangerous in cystic fibrosis patients where sulphur starvation forces the bacterium to rely on de novo cysteine biosynthesis. [1] Adenosine 5'-phosphosulfate reductase (APSR) catalyses an initial step of this pathway, necessary for sulphate assimilation, making it a promising but underexploited target for the development of new antibiotics. Beyond human clinical settings, *P. aeruginosa* represents a critical One Health threat, due to the accumulation of resistant strains in chronic veterinary pathologies with high antibiotic usage (e.g., canine otitis externa, bovine mastitis, equine endometritis).

The flexible C-terminal loop, which enables enzyme catalytic activity, is not present in any experimental structure. [2] Therefore, the missing portion has been reconstructed with AlphaFold2 and the enzyme mechanism has been validated via QM/MM simulations performed with DFT level of theory. [3] The free-energy barrier required to overcome the transition state matches experiments performed on the *Mycobacterium tuberculosis*'s orthologue. [4] Moreover, simulations highlight the important role of the iron-sulphur cluster and its required oxidation state for the enzyme to properly function, in agreement with previous spectrometry experiments. [5]

The validated structure has been then employed to implement a virtual screening workflow consisting of pharmacophore modelling, covalent docking and metadynamics-based rescoring. This systematic and significantly fastened approach was applied to 5.4 million compounds, including four reactive warheads, and resulted in the identification of two active compounds able to inhibit the enzyme with reasonable inactivation efficiencies as starting hit compounds. The activity of the best compound was also confirmed through mass spectrometry identifying the vinylation of the catalytic cysteine and by selecting close analogues for enzymatic assays with similar activity.

Finally, microbiological assays demonstrated the ability to cross the bacterial wall without permeabilizers. The specificity of the inhibition was confirmed through genetic complementation experiments, in which the restoration of the *cysH* gene rescued bacterial growth. While this hit compound necessitates further optimization and improvement of the biological activity, this study underscores the importance of APSR inhibition as new therapeutic strategy against bacterial survival.

REFERENCES

- 1 Tralau et al., J Bacteriol. 2007, 189, 6743-50.
- 2 Chartron et al., J. Mol. Biol. 2006, 364, 152-69.
- 3 Ymeraj et al., Biorxiv 2026, DOI: 10.64898/2026.09.04.749436
- 4 Sun & Leyh. Biochemistry 2006, 45, 11304-11.
- 5 Bhavé et al. Inorg Chem. 2011, 50, 6610–6625

**SMALL-MOLECULE HYDROPHOBIC TAG DEGRADERS AS AN ALTERNATIVE STRATEGY FOR
ANTIPARASITIC DRUG DISCOVERY**

Aurora Gaza,^a Eleonora Diamanti,^a Elisa Uliassi,^a Maria Laura Bolognesi^a, Harry de Koning^b

^a *Department of Pharmacy and Biotechnology, Alma Mater Studiorum – University of Bologna, Via
Belmeloro 6, Bologna 40126.*

^b *School of Infection and Immunity, College of Medical, Veterinary and Life Sciences – University of
Glasgow, Glasgow G43 2DX, U.K.
aurora.gaza2@unibo.it*

Leishmaniasis is a vector-borne parasitic disease caused by *Leishmania* spp. and represents a significant therapeutic challenge. Its spreading is increasing as a consequence of factors including climate change and human mobility, while available treatments are constrained by toxicity, limited efficacy, emerging drug resistance, and restricted accessibility. These limitations underline the unmet medical need for alternative approaches to antiparasitic drug discovery.¹

Targeted Protein Degradation (TPD) represents an event-driven pharmacological modality that differs from conventional occupancy-based inhibition.² Rather than occupying the active site of the protein to block its function, TPD employs small-molecule degraders to promote the removal of selected protein targets by exploiting endogenous cellular degradation pathways. Among these approaches, Hydrophobic Tag (HyT) technology uses hydrophobic moieties to mimic features of misfolded proteins and engage cellular protein quality control (PQC) mechanisms, potentially leading to target protein degradation.³

In this context, the present study investigates a series of twelve HyT degraders designed to target trypanothione reductase (TR), an essential enzyme involved in parasite redox homeostasis and absent from the human host. Despite its established relevance as a potential antileishmanial target, TR presents a broad and relatively featureless active site, which can limit the development of effective conventional inhibitors.⁴ The HyT strategy addresses this challenge by combining a TR-binding ligand with structurally diverse hydrophobic moieties, with the aim of promoting TR recognition by the parasite PQC machinery and ultimately inducing its degradation.

The HyT series was prepared through a multi-step late stage diversification synthesis, allowing diversification of both linker architecture and hydrophobic tag.

Preliminary biological studies revealed a stage-dependent antiparasitic activity within the series against the intracellular amastigote stage of *Leishmania mexicana*. To investigate whether the observed effects are associated with modulation of TR protein levels, CRISPR-Cas9 genome editing was employed to generate a *L. mexicana* cell line expressing Myc-tagged TR.⁵ This engineered model provides a platform for quantitative monitoring of TR abundance by Western blot analysis. Overall, this work provides a biological and mechanistic assessment of small-molecule HyT degraders and investigates their potential as an alternative approach for antiparasitic drug discovery.

REFERENCES

- [1] De Rycker, M., Wyllie, S., Horn, D. et al. *Nat Rev Microbiol.* **2023** vol 21, 35–50
- [2] Espinoza-Chávez RM. et al. *ACS Bio Med Chem Au.* **2022**, 3, 32-45.
- [3] He Q, Zhao X, Wu D. et al. *Eur J Med Chem.* **2023**, 260, 115741.
- [4] Battista, T. et al. *Molecules* **2020**, 25, 1924.
- [5] Beneke T, Gluenz E. *Methods Mol Biol.* **2019**; 1971:189-210

Biocatalytic Valorization of Cashew Nutshell Liquid towards Sustainable Antiparasitic Drug Discovery

Bianca Martinengo,^a Aurora Gaza,^a Harry P. de Koning,^b Maria Laura Bolognesi,^a Daniele Castagnolo^c

^a Department of Pharmacy and Biotechnology, Alma Mater Studiorum - University of Bologna, Bologna 40126, Italy; ^b School of Infection and Immunity, College of Medical, Veterinary and Life Sciences – University of Glasgow, Glasgow G43 2DX, U.K.; ^c Department of Chemistry, University College London, London WC1H 0AJ, U.K.; ^b School of Infection and Immunity, College of Medical, Veterinary and Life Sciences – University of Glasgow, Glasgow G43 2DX, U.K.

bianca.martinengo2@unibo.it

The development of sustainable approaches to drug discovery requires both environmentally compatible synthetic methodologies and renewable sources of chemical diversity. In this context, biocatalysis offers a powerful alternative to conventional synthesis, exploiting the remarkable selectivity of enzymes to perform challenging transformations under mild conditions.¹ Selective oxyfunctionalization is particularly attractive in medicinal chemistry, as it enables the introduction of functional groups into poorly reactive molecular frameworks, providing valuable intermediates for further diversification. Cashew nutshell liquid (CNSL), an abundant agro-industrial by-product of cashew nut processing, represents a renewable source of phenolic lipids bearing a C15 side chain with different degrees of unsaturation. Building on our previous studies exploiting CNSL as a sustainable platform for antiparasitic drug discovery, we investigated biocatalytic oxidative strategies to expand the chemical space accessible from this renewable feedstock. Different enzymatic systems were explored for the selective functionalization of CNSL derivatives. Fungal unspecific peroxygenases (UPOs), versatile heme-thiolate biocatalysts capable of catalysing diverse oxyfunctionalization reactions,² showed limited applicability towards the selected substrates. Conversely, an alternative biocatalytic system based on *Candida antarctica* lipase B (CAL-B) combined with urea hydrogen peroxide (UHP) successfully promoted the selective epoxidation of the unsaturated side chain under mild conditions. This transformation provided functionalized CNSL-derived intermediates suitable for further chemical diversification. The resulting chemical space is currently being explored within an antiparasitic drug discovery framework. Preliminary biological investigations against *Trypanosoma brucei brucei* and *Leishmania mexicana* are providing an initial assessment of the antiparasitic potential of the newly obtained CNSL derivatives. Overall, this work highlights how integrating agro-industrial waste valorization, biocatalysis, medicinal chemistry, and biological evaluation can contribute to more sustainable antiparasitic drug discovery, combining Green Chemistry principles with the broader One Health perspective.³

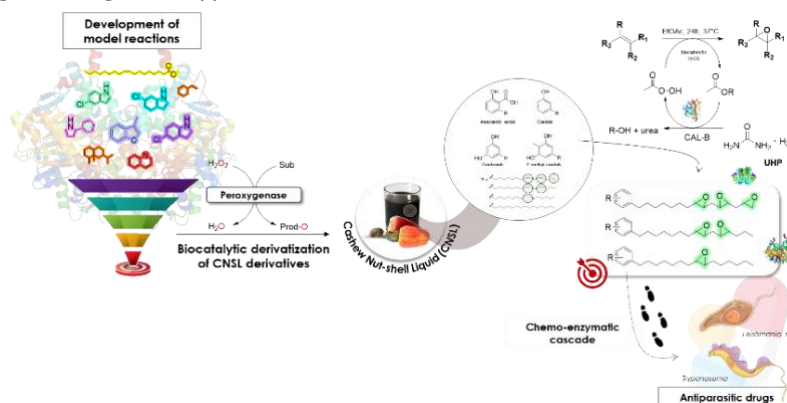


Figure 2 - Biocatalytic derivatization of natural lipids, building blocks, and CNSL derivatives.

REFERENCES

- [1] Winkler, C. K.; et al. *ACS Cent. Sci.* **2021**, 7 (1), 55–71.
- [2] Monterrey, D. T.; et al. *Curr. Opin. Green Sustain. Chem.* **2023**, 41, 100786
- [3] Martinengo, B.; et al. *ACS Infect. Dis.* **2024**, 10, 6, 1856–1870

From Molecular Targets to Drug Repurposing: *In Silico* Strategies for the Discovery of Therapeutic Candidates against Parasitic Vector-Borne Diseases

Biljana Arsić^{a,b,c}, Nada Milić^d, Jovana Janjić^e, Jan Baumbach^c, Jill Barber^b

^a University of Niš, Faculty of Sciences and Mathematics, Department of Chemistry, Niš, Serbia;

^b University of Manchester, School of Health Sciences, Division of Pharmacy and Optometry, Manchester, United Kingdom;

^c University of Hamburg, Institute for Computational Systems Biomedicine, Hamburg, Germany;

^d University of Szeged, Faculty of Sciences and Informatics, Szeged, Hungary;

^e University of Belgrade, Faculty of Biology, Belgrade, Serbia.

biljana.arsic@pmf.edu.rs

Parasitic vector-borne diseases, including malaria, visceral leishmaniasis and dengue, remain important global health challenges, while the development of new therapeutic agents is often limited by the high cost, lengthy timelines and biological complexity of conventional drug discovery. Our research has focused on the application and integration of computational approaches to identify and prioritize potential therapeutic candidates against these diseases.

Our early studies focused on the structural characterization and modelling of potential molecular targets in *Plasmodium falciparum*, including components of the apicoplast ribosome,¹ providing structural models for subsequent structure-based drug discovery. This approach was further extended to the investigation of erythromycin B derivatives, combining molecular docking with experimental evaluation of their antimalarial activity against a multidrug-resistant *P. falciparum* strain.²

More recently, our work has moved towards integrated drug repurposing strategies for parasitic vector-borne diseases. Electron-ion interaction potential (EIIP)-guided virtual screening, molecular docking, molecular dynamics simulations, MM-GBSA binding free-energy calculations, network-based drug repurposing and *in silico* ADMET profiling have been combined to identify and prioritize clinically relevant compounds against *Leishmania donovani* and dengue virus.^{3,4}

The overall objective of our research is to develop an integrated computational framework that connects target identification and structural modelling with drug screening, repurposing, network-based analysis and pharmacokinetic prioritization.

REFERENCES

- [1] Arsic, B. and Barber, J. *Chemia Naissensis* **2019**, 2(2), 50-61.
- [2] Bhadra, P. K. *et al. Materials* **2021**, 14, 6980.
- [3] Arsić, B. *Pharmaceutics* **2025**, 17, 1021.
- [4] Ilić, B. S. *et al. Open Chem.* **2026**, 24(1), 20250273.

Development of Novel Thiazolopyrimidine Derivatives Active Against Visceral and Cutaneous Leishmania

Gülşah Bayraktar¹, Merve Saylam², Pascal Marchand³, Huseyin Istanbulu⁴

¹Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ege University, Bornova, 35100, Izmir, Turkey, gulsah.bayraktar@ege.edu.tr, bayraktargulsah@gmail.com

²Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Izmir Katip Celebi University, Cigli, 35620, Izmir, Turkey

³Cibles et Médicaments des Infections et de l'Immunité, IICiMed, Nantes Université, UR 1155, F-44000 Nantes, France

As a major neglected tropical disease, leishmaniasis is etiologically linked to *Leishmania* species and is transmitted via the phlebotomine sandfly vector. Clinical spectrum of Leishmaniasis ranges from the potentially fatal visceral form to cutaneous and mucocutaneous leishmania. Current therapeutic approaches are highly limited due to poor therapeutic index and emerging resistance. Although pentavalent antimonials remain the primary treatment option, their use is frequently restricted by severe systemic toxicities. Secondary options, including liposomal amphotericin B, miltefosine, and pentamidine, offer alternatives but are often limited by stability, cost, or administration challenges.

Given the high rate of treatment failure of existing drugs, the identification novel, selective, safe and cost-effective medications are urgently needed.

In this context, our research groups have been working extensively for the development of a new generation of more effective and safer antileishmanial agents with a new mechanism of action to limit the devastating impact of parasite resistance. We have previously reported a series of thiazolopyrimidine derivatives as a *Leishmania major* pteridine reductase 1 (*LmPTR1*) enzyme inhibitor with *in vitro* antileishmanial activity against promastigote forms and low cytotoxicity [1]. Later, antileishmanial activities against *L. donovani* and *L. major* axenic amastigotes, intramacrophage amastigotes and cytotoxicity on macrophages of novel thiazolopyrimidine entities were introduced [2]. Lastly, original compounds bearing thiazolopyrimidine core with *in vivo* efficacy on visceral leishmaniasis and cutaneous leishmaniasis models in BALB/c mice were developed [3].

Our expertise on these types of compounds was merged with Prof. Pascal Marchand's research groups expertise thanks to a Short-Term Scientific Mission within Cost Action 21111-OneHealthdrugs to explore the chemical diversity of the novel derivatives with good selectivity index and antileishmanial activity on visceral and cutaneous strains. This collaboration led to a new international, multidisciplinary project for the pursuit of the development of effective, selective and safer novel chemical entities for the treatment of Leishmaniasis.

Considering the importance of the toxicity of the novel compounds in the early stage of the drug discovery within one health framework, our research efforts is continuing in our laboratories.

REFERENCES

1. Istanbulu, Huseyin, et al. "Design, synthesis, and in vitro biological evaluation of novel thiazolopyrimidine derivatives as antileishmanial compounds." *Archiv der Pharmazie* 353.8 (2020): 1900325.
2. Bayraktar, Gulsah, et al. "Biological properties and in silico studies of thiazolopyrimidine derivatives active against visceral and cutaneous leishmania spp. amastigote forms." *European Journal of Medicinal Chemistry Reports* 12 (2024): 100228.
3. Istanbulu, Huseyin, et al. "Design, synthesis, in vitro–In vivo biological evaluation of novel thiazolopyrimidine compounds as antileishmanial agent with PTR1 inhibition." *European Journal of Medicinal Chemistry* 247 (2023): 115049.



One Health drugs against parasitic vector borne diseases in Europe and beyond
OneHealthdrugs

Cost Action CA21111

From Belgian Cattle to Japanese Deer: Prevalence, Drug Susceptibility and Genomic Diversity of *Trypanosoma theileri*

Stijn Verhoeven,^a Guy Caljon,^a Kayhan Ilbeigi,
stijnverhoeven15@gmail.com

Trypanosoma theileri is a widespread bovine trypanosome that remains relatively understudied despite its broad geographical distribution and occurrence in both livestock and wildlife hosts. During a Belgian sampling campaign conducted as part of a Master's thesis, cattle were screened for *T. theileri* using two complementary approaches. Molecular detection was used to determine the presence of *T. theileri* DNA, while parasite isolation and in vitro cultivation provided a parasitological assessment of prevalence and enabled the establishment of viable Belgian cattle-derived isolates. Comparing these molecular and cultivation-based approaches provided insight into the occurrence of *T. theileri* in Belgian cattle while simultaneously generating parasite material for further characterization. Successfully established Belgian isolates are currently being evaluated in ongoing in vitro drug susceptibility screening to characterize their responses to selected antitrypanosomal compounds. In parallel, genetic and genomic analyses were initiated to investigate diversity and evolutionary relationships among the Belgian cattle-derived strains. Building on this work, collaboration was established with the National Research Center for Protozoan Diseases (NRCPD), Obihiro University of Agriculture and Veterinary Medicine, Japan, which maintains *T. theileri* isolates originating from Japanese deer. This collection provides a unique opportunity to compare Belgian cattle-derived and Japanese deer-derived *T. theileri* and to investigate genetic diversity across geographically and biologically distinct parasite populations. Comparative genetic and genomic analyses will focus on the relationships between these isolates and their divergence from available reference strains, with particular interest in geographical diversity and potential host-associated differences. By integrating Belgian epidemiological sampling, molecular and parasitological detection, ongoing drug susceptibility profiling, and comparative genetic analysis, this work provides a comprehensive characterization of Belgian *T. theileri* isolates and establishes a framework for investigating the diversity, evolution and potential host adaptation of *T. theileri* across European livestock and Japanese wildlife populations.



Figure 3 - Microscopic visualization of *Trypanosoma theileri* parasites detected in two of the four positive cultures established from Belgian cattle samples.

Valorization of Cashew Nut Shell Liquid for Sustainable Antiviral Drug Discovery via the Ugi 4-Component Reaction

Filippo Piazza,¹ Valeria Napolitano,² Francesca Esposito,³ Rita Berisio,² Enzo Tramontano,³ Eleonora Diamanti,¹ and Maria Laura Bolognesi¹

1 Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy 2 National Research Council, Naples, Italy

*3 Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy
filippo.piazza7@unibo.it*

Keywords: Antiviral, MCR, Green Chemistry, Agro-industrial waste, CNSL

The use of biowaste in medicinal chemistry as source for the development of new drug candidates has gained considerable attention in recent years. Here, we envisage the use of Cashew Nutshell Liquid (CNSL)¹ as a renewable starting material for the development of novel and sustainable antiviral inhibitors. Our endeavours focus on treating infections caused by the West Nile Virus (WNV), a disease that is becoming increasingly prevalent in Western countries due to megatrends, with Italy being one of the main hotspots. In view of the rapid spreading of the virus, the absence of a medical treatment and the severe consequences of such infections, medicinal chemistry efforts are urgently needed. In this context, we pioneer the use of CNSL as starting material that is functionalized in a single step *via* the Ugi four-component (U-4C)² reaction to efficiently deliver a green library of antiviral small molecule inhibitors.

Specifically, we are synthesizing bio-based CNSL derivatives targeting the active site of the NS2B-NS3 protein, an essential enzyme for viral replication for which crystallographic data are available.³ Moreover, this pocket is conserved among West Nile, Dengue and Zika viruses opening the possibility of developing *pan*-antiviral small molecules. Considering that the active site consists of a catalytic triad made by serin, histidine and aspartate, we envisioned incorporating basic functional groups to enhance binding affinity toward the target. Furthermore, since most reported NS2B-NS3 protease inhibitors are substrate-derived peptidomimetics,⁴ we believe that adopting the Ugi-4CR reaction, which directly affords peptide-like scaffolds, represents a strategic synthetic approach. So far, we managed to optimize the synthetic scheme in a green chemistry fashion with one component of the Ugi-4-C coming directly from CNSL, while the other three introduced in a sustainable manner. We made a subset of around 30 differently substituted derivatives featuring chemically diverse branched substituents on the scaffold.

Importantly, we obtained the co-crystal structure at 1.8 Å strengthening our design strategy.

Preliminary screening of a first series of the synthesised compounds led to conclude that most rigid derivatives are better tolerated than the more flexible analogues with the most promising candidates having IC₅₀ values of around ≈ 70 μ M. Based on these initial findings, we are enriching our library with novel derivatives to further increase the affinity toward the target. By fulfilling two of the Green chemistry principles⁵ (#2 and #7), our results highlight the potential of CNSL-derived compounds as safe, effective and environmentally friendly anti-infective agents.

They also promote waste valorisation and local drug production, while aligning with global sustainable development goals.

One Health drugs against parasitic vector borne diseases in Europe and beyond
OneHealthdrugs

Cost Action CA21111

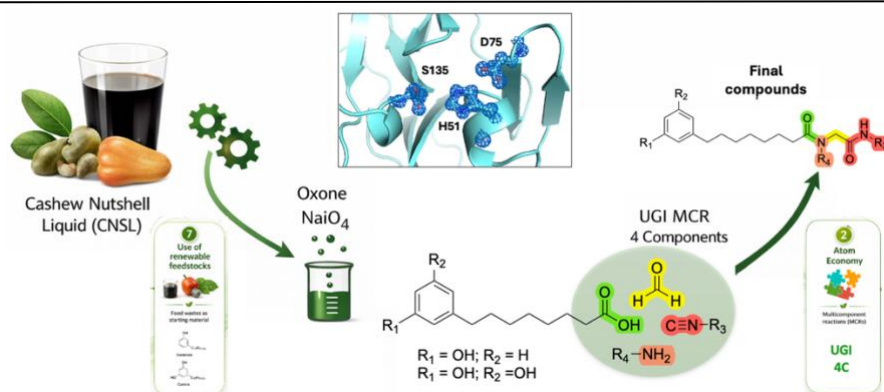


Figure 4: Sustainable drug discovery workflow from CNSL to antivirals targeting the NS2B/NS3 serine protease.

References:

- [1] B. Martinengo..., M.L. Bolognesi. Sustainable Antiparasitic Agents from an Agro-Industrial Waste: Mitochondria-Targeting Cashew Nutshell Liquid-Derived Phosphonium and Ammonium Salts. *J. Med. Chem.* 2025, 68, 19438–19462.
- [2] A. Dömling, I. K. Ugi. Multicomponent Reactions with Isocyanides. *Angew. Chem. Int. Ed.* 2000, 39, 3168–3210.
- [3] J. Lei, R. Hilgenfeld. Crystal structure of Zika virus NS2B-NS3 protease in complex with a boronate inhibitor. *Science* 2016, 353, 503–5.
- [4] Saan Voss, Christoph Nitsche. Targeting the protease of West Nile virus. *RSC Med Chem*, 2021, 12(8), 1262–1272.
- [5] P. Anastas, N. Eghbali. *Green Chemistry: Principles and Practice*. *Chem Soc Rev*, 2010, 39, 301–312.