

PROGRAM AND BOOK OF ABSTRACTS



Institutions responsible for the organization



Anniversary Online Symposium

September 14-15, 2026

Foreword

Dear members and affiliates of ResNet NPND, Dear colleagues and friends,

It is a great pleasure to welcome you all to the International Symposium on Neglected Diseases Drug Discovery – ISyND3: Advances in ResNet NPND and Global Collaborations. It is an honor to celebrate, together with all of you, the 15th anniversary of our Research Network on Natural Products Against Neglected Diseases. Since the memorable meeting held at the University of Münster in April 2011, ResNet NPND has followed a remarkable trajectory, characterized by collaboration, scientific commitment, and the continuous search for solutions to address neglected diseases. Over the years, our Network has grown stronger and expanded its international reach, currently comprising 45 affiliated members from 16 countries. This significant development demonstrates the strength of scientific cooperation and collective effort. By bringing together institutions, fields of knowledge, and diverse experiences, we have contributed to the advancement of research, as reflected in our scientific publications, as well as, in the identification and characterization of natural products and molecules with potential for the development of new therapeutic strategies against neglected tropical diseases.

The organization of this symposium, held online, is also the result of an important collaborative effort. We would like to express our gratitude to everyone who contributed to the development of a high-level scientific program for this event. The carefully prepared program addressed a diverse range of current topics, including medicinal chemistry, drug repurposing, biodiversity, plant metabolites, and natural products, which are relevant and strategic to the future of research and innovation in the field of neglected diseases. We hope that these two days will be intense and enriching, marked by the exchange of knowledge, the sharing of experiences, productive discussions, and the establishment of new partnerships and perspectives for our Network. We hope that this meeting will further strengthen the bonds among participants and inspire new initiatives capable of generating scientific and social impact. We would like to thank everyone whose presence and commitment have made this symposium possible. It is a great pleasure to welcome you to ISyND3. We wish you all an excellent event, filled with meaningful learning opportunities, fruitful discussions, and significant advances in science and in the global fight against neglected diseases.

Thank you very much, and we wish you all an excellent symposium.

Mário Steindel and Louis Pergaud Sandjo

Florianópolis, September, 14-15, 2026.

1. Program

International Symposium on Neglected Diseases Drug Discovery (ISyND3)

Advances in ResNet NPND and Global Collaborations

Logistics Panel

Modality: Virtual

Date: 14 and 15 September 2026



September 14th 2026 am

7:00	Opening
7:45 - 7:50	Wellcome - Prof. Dr. Mario Steindel
8:00 – 8:30	Lecture 1 - Fifteen Years of ResNet NPND – A Brief History and a Success Story: Repositioning of a Herbal Medicine as a New Hope for a Neglected Tropical Disease Prof. Dr. Thomas Schmidt - WWU Münster, Germany - Coordinator of ResNet NPND
Section 1	Biodiversity, Plant metabolites, Synthetic strategies, and NTDs drug discovery
8:40 – 8:55	From Plant Metabolites to Intracellular Antileishmanial Activity: Galloylated Flavan-3-ols from <i>Acacia nilotica</i> against <i>Leishmania donovani</i> Prof. Dr. Sami A. Khalid - Faculty of Pharmacy, University of Science and Technology (UST), Omdurman, Sudan

8:55 – 9:10	Antivenom Potential fo <i>Vernonia glabrata</i> and <i>Combretum collinum</i> , Medicinal Plants Used in the Management of Snakebite Envenomation in Nyatike Sub-Country, Kenia Prof. Dr. Prince Ojuka - Department of Physical Sciences, University of Embu, Embu, Kenya
9:10 – 9:25	Mas Spectrometry-Based Profiling of Small Molecules: Applications in Metabolomics and Natural products Research Prof. Dr. Hyung Min Kim - College of Pharmacy, Chungnam National University, Republic of Korea
9:25 – 9:40	Marine and Extremophilic Microbial Compounds as Promising Hits for Chagas Disease Prof. Dr. André Tempone - Instituto Butantan, São Paulo, Brazil
9:40 – 10:10	Open to questions
10:10 – 10:40	Lecture 2 - Life is Heterocyclic – Chemical Contribution to Fighting and Preventing Diseases Prof. Dr. Till Opatz - Department of Chemistry, Johannes Gutenberg University, Duesbergweg, Mainz, Germany
Section 2	Scientific exchange and Protein target-guided NTDs drug discovery
10:50 – 11:05	Drug Development for Encephalitic and Arthritogenic Infections Caused by Alphaviruses Prof. Dr. Victor Ogungbe - Chemistry and Biotechnology Science and Engineering Program, College of Science, University of Alabama, Huntsville, USA
11:05 – 11:20	One-atom exchange-enabled reversibility of covalent inhibition yields selectivity in Cathepsin S fluorescent probes Mr. Thales do Valle Moreira - Institut für Pharmazeutische und Biomedizinische Wissenschaften, Johannes Gutenberg University of Mainz, Germany
11:20 – 11:35	Design and Synthesis of Novel AKAP-PKA-Disruptors Mr. Niklas Ehlenz - Department of Chemistry, Johannes Gutenberg University, Duesbergweg, Mainz, Germany
11:35 – 12:05	Open to questions
12:05 – 13:20	Lunch time
September 14th 2026 pm	
Section 3	Drug repositioning in NTDs drug discovery
13:30 – 13:45	Indirubin as a promising antileishmanial agent against <i>Leishmania infantum</i> amastigotes Ms. Mariza Gabriela Faleiro de Moura Lodi Cruz - Grupo Genômica Funcional de Parasitos (GFP) Instituto René Rachou/ IRR- Fiocruz Minas, Brazil
13:45 – 14:00	The use of Glimepiride through the drug repositioning approach and its in vitro action against <i>Leishmania infantum</i> Ms. Karen Daniela da Silva Melo - Grupo Genômica Funcional de Parasitos (GFP) Instituto René Rachou/ IRR- Fiocruz Minas, Brazil
14:00 – 14:15	Antileishmanial activity of quercetin against <i>Leishmania infantum</i> amastigotes Ms. Giovanna Cecília de Paula e Sá - Grupo Genômica Funcional de Parasitos (GFP) Instituto René Rachou/ IRR- Fiocruz Minas, Brazil
14:45 – 15:15	Open to questions
15:15 – 16:30	Discussion on the Network's Perspectives and Future Directions
	Discussion on the Network's Perspectives and Future Directions. (14:45-16:30) <pre> graph LR A[Open our box of old anti-NTDs leads.] --> B[Create a secure sandbox where we share these old leads.] B --> C[Create collaborative work packages to revisit these leads (inspire new design, bioassay in vitro, in vivo)] C --> D[Sign an agreement. Collaborative projects.] D --> E[How to make it accessible to everyone] </pre>

September 15th 2026 am	
8:00 – 8:30	Lecture 3 - Covalency in Enzyme Inhibition Prof. Dr. Tanja Schirmeister - Institute of Pharmaceutical and Biomedical Sciences, Staudingerweg, Mainz, Germany
Section 4	Natural product-inspired NTDs drug discovery
8:40 - 8:55	The effect of <i>Chromolaena hookeriana</i> and <i>Campuloclinium macrocephalum</i> (Asteraceae) extracts against <i>Trypanosoma cruzi</i> and <i>Leishmania amazonensis</i> in vitro Ms. Ludmila Ferreira de Almeida Fiuza - Laboratório de Biologia Celular, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
8:55 – 9:10	Antileishmanial and antimalarial activities of synthetic endoperoxide derived from marine natural products Prof. Dr. Sébastien Pomel - Université Paris-Saclay, CNRS, BioCIS, France
9:10 – 9:25	<i>In Vitro</i> Antitrypanosomal Activity of Compounds Isolated from the Leaves of <i>Funtumia elastica</i> (Preuss) (Apocynaceae) Ms. Kom M. Larissa - Centre for Research on Medicinal Plants and Traditional Medicine (CPRMT), Institute of Medical Research and Medicinal Plants Studies (IMPM), Yaoundé, Cameroon
9:25 – 9:40	Desing and synthesis of clickable cationic alkaloids Mr. Cory Laurent
9:40 – 10:10	Open to questions
10:10 – 10:40	Lecture 4 - Exploring Brazilian Floristic Biodiversity for the Discovery of Natural Product-Based Prototypes against Neglected Tropical Diseases. Prof. Dr. João Henrique Ghilardi Lago –
Section 5	Session 6: Phytochemicals as a source of new drugs against parasitic diseases:
10:50 – 11:05	Antileishmanial and Cytotoxic Activities of Phytochemicals from the Leaves of <i>Tectona grandis</i> Linn. (Verbenaceae) Prof. Dr. Théodora Kopa - Centre for Research on Medicinal Plants and Traditional Medicine (CPRMT), Institute of Medical Research and Medicinal Plants Studies (IMPM), Yaoundé, Cameroon
11:05 – 11:20	Exploring the antiparasitic potential of <i>Cannabis sativa</i> against cystic echinococcosis Ms. Florencia Gatti - Grupo de Farmacoterapia Experimental; Instituto de Investigaciones en Producción, Sanidad y Ambiente (IIPROSAM, CONICET-UNMdP); Facultad de Ciencias Exactas y Naturales; Universidad Nacional de Mar del Plata; Argentina
11:20 – 11:35	Antiprotozoal Aminosteroid Alkaloids from <i>Buxus obtusifolia</i> : Chemical Diversity, Bioactivity, and Seasonal Variation Dr. Justus W. Mukavi - University of Münster, Institute of Pharmaceutical Biology and Phytochemistry (IPBP), PharmaCampus, Corrensstraße, Münster, Germany
11:35 - 11:50	Hit-to-lead optimization of benzenesulfonyl derivatives: activity as anti-Trypanosomatidae agents Dr. Daniela de Melo Resende - Grupo Genômica Funcional de Parasitos (GFP) Instituto René Rachou/ IRR- Fiocruz Minas, Brazil
11:50 – 12:20	Open to questions
12:20 – 13:20	Lunch time
September 15th 2026 pm	
Section 6	Pavement to clinical phase
13:30 – 14:00	Lecture 5 - From Molecule Selection to Clinical Phase I: A Long and Challenging Journey Prof. Dr. João Batista Calixto - Centro de inovação e Ensaios Pré-clínicos (CIEnP), Florianópolis SC, Brazil
14:10 – 14:25	Exploring Ibero-American Edible Asteraceae Species against <i>Trypanosoma brucei</i> Mr. Nicolas Perez Mauad - CONICET–Universidad de Buenos Aires, Instituto de Química y Metabolismo del Fármaco (IQUIMEFA), Buenos Aires, Argentina
14:25 – 14:40	Screening of Edible Species from Ibero-America for Antileishmanial Activity against <i>Leishmania panamensis</i> Ms. Laura C. Laurella - Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Buenos Aires, Argentina
14:40 – 15:00	Open to questions

15:00 – 15:30	Lecture 6 – Navigating chemical space to develop treatments for infectious diseases. Prof. Dr. Rafaela Salgado Ferreira
15:40 – 16:30	Final exchange and end of the symposium

ABSTRACTS

Fifteen Years of ResNet NPND – A brief History and a Success Story: Repositioning of a Herbal Medicine as a New Hope for a Neglected Tropical Disease

Thomas J. Schmidt

University of Münster, Institute of Pharmaceutical Biology and Phytochemistry, PharmaCampus – Corrensstrasse 48, 48149 Münster, Germany

Fifteen years have passed since the seminal meeting of researchers from Brazil, Germany and a few other countries at the University of Münster which resulted in the foundation of the Research Network Natural Products against Neglected Diseases. On this occasion, it appears appropriate to present a brief historic overview of the work in the network done in these years. It should be allowed to focus on one successful, and still ongoing, ResNet NPND project involving my own group, in cooperation with that of Sara M. Robledo (Medellin, Colombia), in which an approved European herbal medicine with a long tradition is being repurposed for the treatment of a serious neglected tropical disease (NTD). Arnica flowers (*Arnicae flos* Ph. Eur., flowerheads of *Arnica montana* L., Asteraceae) are used in phytotherapy as traditional remedies against symptoms of blunt trauma and inflammatory processes of the muscles/skeleton and skin. We have discovered a very good efficacy of Arnica tincture (Ph. Eur.) against cutaneous leishmaniasis (CL), an NTD caused by parasites of the genus *Leishmania* and transmitted by sandflies. The therapeutic effect was thoroughly documented and characterized in detailed chemical, biochemical, *in vitro* as well as *in vivo*-experiments [1-4]. A first clinical study with human CL patients could then be accomplished with great success [4]. An extended clinical study is currently in progress. The outcome of this research gives rise to the hope that Arnica tincture may soon be established as a new effective, safe and affordable therapy for this severe neglected tropical disease.

References

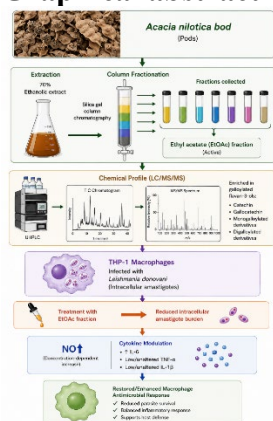
1. Jürgens FM, Herrmann FC, Robledo SM, Schmidt TJ. Dermal Absorption of Sesquiterpene Lactones from Arnica Tincture. *Pharmaceutics* 2022, 14, 742. DOI: 10.3390/pharmaceutics14040742
2. Jürgens FM, Robledo SM, Schmidt TJ. Evaluation of Pharmacokinetic and Toxicological Parameters of Arnica Tincture after Dermal Application In Vivo. *Pharmaceutics* 2022, 14, 2379. DOI: 10.3390/pharmaceutics14112379
3. Robledo SM, Murillo J, Arbeláez N, Montoya A, Ospina V, Jürgens FM, Vélez ID, Schmidt TJ. Therapeutic efficacy of Arnica in hamsters with cutaneous leishmaniasis caused by *Leishmania braziliensis* and *L. tropica*. *Pharmaceutics* 2022, 15, 776; DOI: 10.3390/ph15070776
4. Robledo SM, López L, Quintero J, Tabares Y, Garcés AC, Rios S, Soto E, Vélez ID, Schmidt TJ. A phase Ib/II clinical study to evaluate the safety and efficacy of topical Arnica tincture to treat non-complicated Cutaneous Leishmaniasis in Colombia. *PLoS Negl Trop Dis* 2025, 19, e0013123. DOI: 10.1371/journal.pntd.0013123

From Plant Metabolites to Intracellular Antileishmanial Activity: Galloylated Flavan-3-ols from *Acacia nilotica* against *Leishmania donovani*

Nada Mustafa El-Khatim^{1,2}, Maowia M. Mukhtar^{1,2}, Amal Al Dawi^{1,2}, Thomas J. Schmidt³, Sami A. Khalid^{4*}

¹ Bioscience Research Institute, Khartoum, Sudan; ² Institute of Endemic Diseases, University of Khartoum, Khartoum, Sudan; ³ Institute of Pharmaceutical Biology and Phytochemistry, University of Münster, Germany ⁴ Faculty of Pharmacy, University of Science and Technology (UST), Omdurman, Sudan.

Graphical abstract



Abstract

Visceral leishmaniasis is yet a major neglected tropical disease for which safer and more effective therapeutics are urgently needed. We investigated the antileishmanial potential of chemically distinct fractions obtained from *Acacia nilotica* pods, with particular emphasis on the clinically relevant intracellular amastigote stage of *Leishmania donovani*. We evaluated the chloroform and ethyl acetate fractions against promastigote and intracellular amastigote stages of *L. donovani* and *L. major*. The ethyl acetate fraction showed marked activity against intracellular *L. donovani* amastigotes (IC₅₀ approximately 10 µg/mL), whereas the chloroform fraction was essentially inactive (IC₅₀ >1000 µg/mL). UHPLC-(+)-ESI-QTOF-MS profiling distinguished the active ethyl acetate fraction by enrichment in flavan-3-ol-related metabolites, including catechin, gallic acid, and mono- and digalloylated derivatives. In infected THP-1 macrophages, treatment was associated with concentration-dependent nitric oxide production and modulation of cytokine responses, including increased IL-6 with comparatively low TNF-α and IL-1β concentrations. Together, the chemical and biological data show that galloylated flavan-3-ols may contribute importantly to the intracellular antileishmanial activity of the ethyl acetate fraction. These observations support further bioassay-guided isolation and structural characterization of individual metabolites to define structure-activity relationships and to distinguish parasite-directed effects from modulation of macrophage antimicrobial responses. *Acacia nilotica* therefore constitutes a prospective source of chemically diverse natural-product leads for antileishmanial drug discovery. At the same time, purified-compound studies are required to establish the constituents responsible for activity and their mechanisms. The marked selectivity between the two fractions provides a useful chemical-biological starting point for prioritizing active constituents, integrating natural-product profiling directly with disease-relevant intracellular phenotypic assays.

Keywords: *Acacia nilotica*; *Leishmania donovani*; visceral leishmaniasis; galloylated flavan-3-ols; intracellular amastigotes; natural-product drug discovery.

Antivenom Potential of *Vernonia glabra* and *Combretum collinum*, Medicinal Plants Used in the Management of Snakebite Envenomation in Nyatike Sub-County, Kenya

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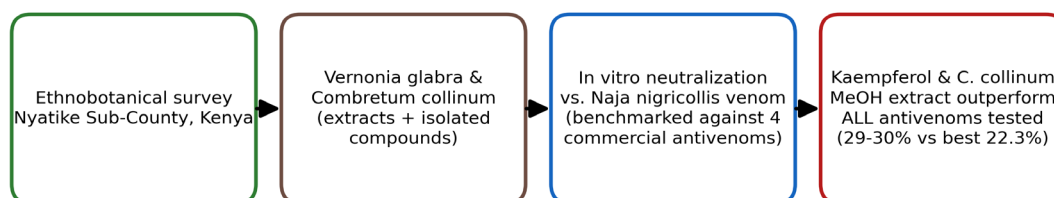
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Graphical Abstract



Abstract

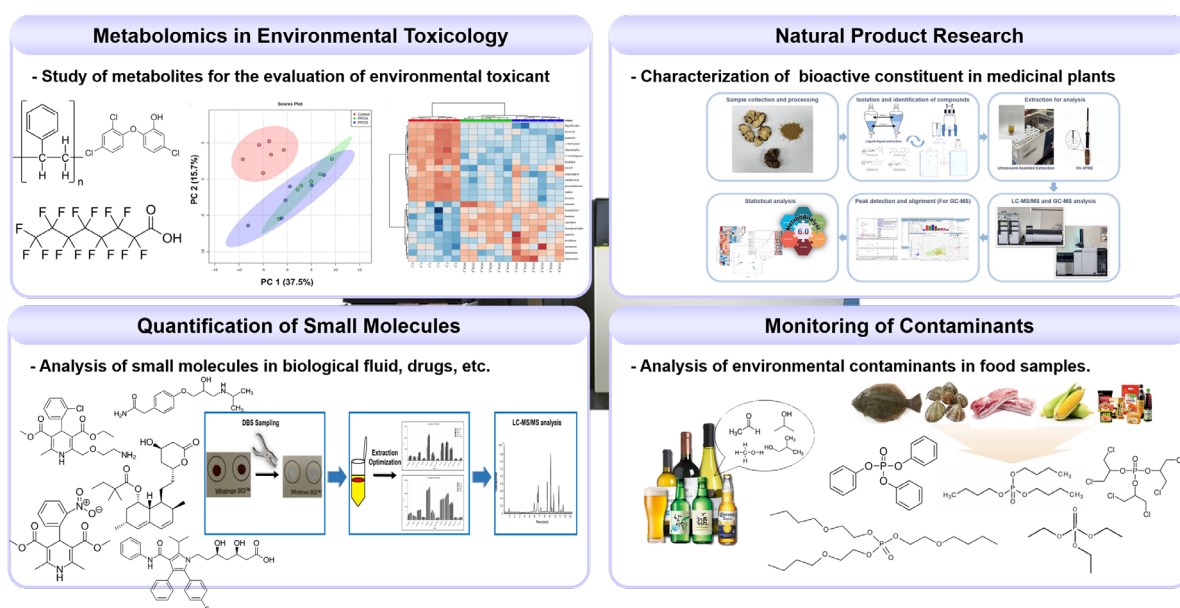
Snakebite envenomation is a major yet neglected public health burden in rural sub-Saharan Africa, where limited access to antivenom drives continued reliance on traditional medicinal plants. In Nyatike Sub-County, Kenya, ethnobotanical surveys identified *Vernonia glabra* and *Combretum collinum* among the plants most frequently used by local healers to manage snakebite. This study evaluated the *in vitro* venom-neutralizing activity of extracts and isolated compounds from both species against *N. nigricollis* venom, benchmarked against four commercial antivenoms (PANAF-Premium, EchiTab-Plus-ICP, PAN AFRICA Inoserp, and Snake Venom Antiserum African HIS). The methanol extract of *C. collinum* and the isolated flavonoid kaempferol (from *V. glabra*) significantly reduced venom-induced activity and outperformed all four commercial antivenoms tested. *In vivo* cytotoxicity screening using the *Artemia salina* lethality assay showed that all extracts and isolated compounds were markedly less toxic than the venom itself and the vincristine sulphate cytotoxic control, with 24-hour LC₅₀ values ranging from 154.7 to 2698.1 µg/mL for the plant-derived samples versus 19.8 µg/mL for venom and 5.1 µg/mL for vincristine sulphate. These findings provide strong early pharmacological validation of ethnobotanical knowledge documented in Nyatike Sub-County. The results identify these medicinal plants as a promising, low-toxicity lead compound with venom-neutralizing activity exceeding currently available commercial antivenoms.

Mass Spectrometry-Based Profiling of Small Molecules: Applications in Metabolomics and Natural Product Research

Hyung Min Kim

College of Pharmacy, Chungnam National University, Republic of Korea

Research Field: Analytical Chemistry based on Mass Spectrometry



Our laboratory develops mass spectrometry-based profiling strategies for small molecule characterization, applying a common analytical and chemometric framework across two complementary research areas. Using LC-MS/MS (TSQ Altis, Agilent Revident QToF) and GC-MS platforms, we perform untargeted and targeted metabolite profiling combined with multivariate statistics to extract biologically meaningful patterns from complex spectral data. First, in environmental toxicology, we apply metabolomic profiling to model organisms such as *Caenorhabditis elegans* to characterize metabolic perturbations induced by environmental toxicants, linking chemical exposure to underlying biochemical mechanisms. Second, in natural product research, we apply the same profiling and chemometric workflow to authenticate geographical origin, assess quality, and characterize bioactive constituents of medicinal plants and natural products, supporting both regulatory and industrial applications. Across both domains, small molecule profiling serves as a unifying analytical strategy, translating raw mass spectral data into interpretable chemical and biological insight. This presentation introduces our profiling workflow and representative case studies from environmental toxicology and natural product research, highlighting the versatility of a single mass spectrometry-based platform across distinct application contexts.

Marine and Extremophilic Microbial Compounds as Promising Hits for Chagas Disease

Andre Gustavo Tempone¹ & João Henrique G. Lago²

1. Instituto Butantan, São Paulo, Brazil

2. Federal University of ABC, São Paulo, Brazil

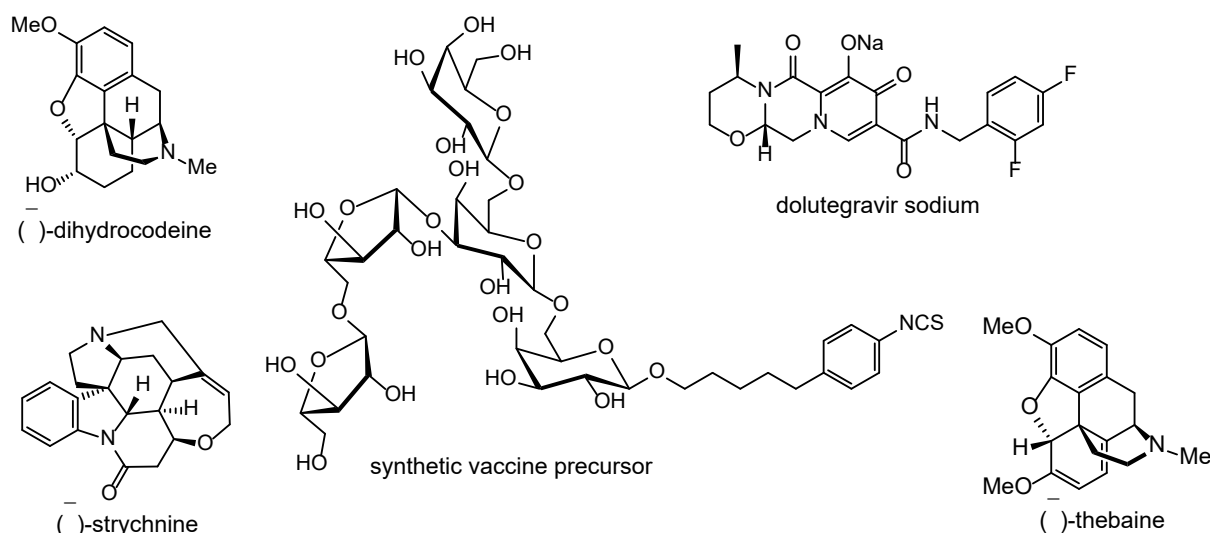
andre.tempone@butantan.gov.br; joao.lago@ufabc.edu.br

Chagas disease is a neglected tropical disease caused by the protozoan parasite *Trypanosoma cruzi*. Predominantly affecting vulnerable populations, it remains a major public health challenge, particularly in Latin America. Current treatment has important limitations, including toxicity, adverse effects, and variable efficacy, particularly during the chronic phase of the disease, highlighting the urgent need for safer and more effective therapies. Natural products represent a valuable source of structurally diverse bioactive compounds, while marine and extreme environments harbor remarkable chemical diversity that remains largely underexplored. Our studies have focused on the bioprospecting of marine organisms and microorganisms as sources of antitrypanosomal compounds. Extracts, fractions, and metabolites obtained from marine sponges, corals, and associated bacteria collected from Brazilian coastal and oceanic environments were evaluated against *T. cruzi*. In parallel, bacteria isolated from extreme environments in Chilean Patagonia, characterized by high salinity, alkaline pH, and low temperatures, were investigated as sources of specialized metabolites with antitrypanosomal potential. Several samples exhibited promising activity against clinically relevant parasite stages, particularly intracellular amastigotes. Bioactivity-guided fractionation led to the isolation of structurally diverse metabolites, including alkaloids, cyclic lipopeptides such as surfactins, and iso-fatty acids, all of which exhibited activity against intracellular amastigotes of *T. cruzi*. Collectively, these findings reinforce the importance of marine biodiversity and extremophilic microbial chemodiversity for the discovery of novel antitrypanosomal scaffolds. The identified compounds represent promising starting points for medicinal chemistry, mechanism-of-action, and pharmacokinetic studies aimed at developing new drug candidates for Chagas disease. Supported by FAPESP 2024/16243-4

Life is Heterocyclic – Chemical Contributions to Fighting and Preventing Prevalent Diseases

Alexander Lipp, Jule P. Dietz, Matthias Krumb, Danuta Kowalczyk, Leander Geske, Rainer Wiechert, Anthony J. Arduengo, III, Siegfried R. Waldvogel, Till Opatz*

Department of Chemistry, Johannes Gutenberg University, Duesbergweg 10-14, 55128 Mainz, Germany



Heterocycles play a key role in the machinery of life and it is not surprising that heterocyclic compounds are also privileged structural elements contained in most pharmaceuticals. The seminar highlights new developments in the construction of heterocyclic compounds, in the total synthesis of bioactive natural products (e.g. opium alkaloids and strychnine) and their derivatives.

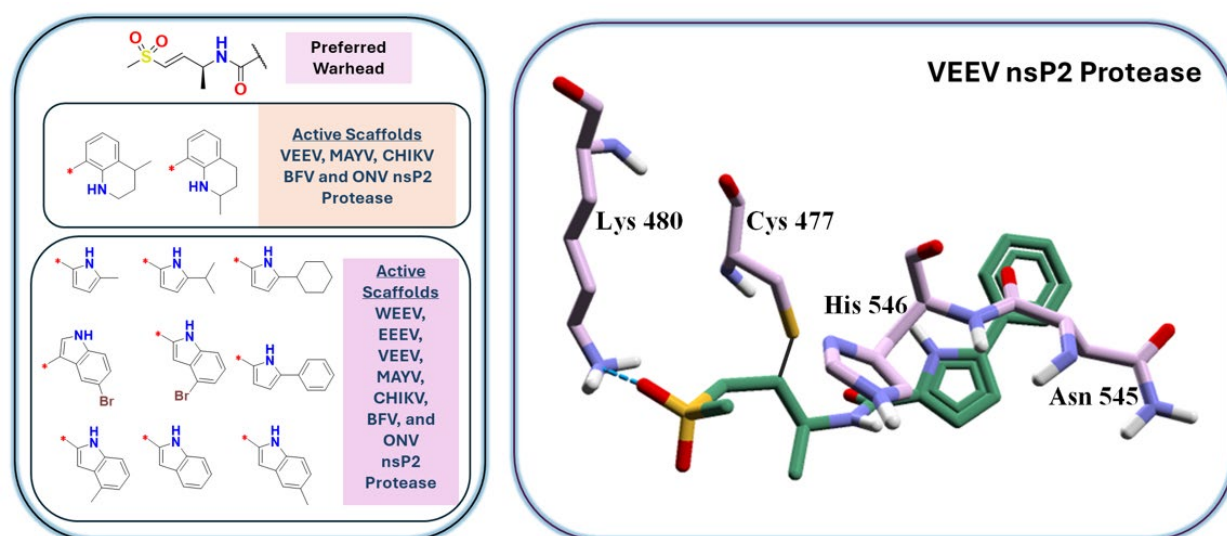
Economic alternative syntheses of important antiinfectives developed in the course of the “Medicines for All” initiative of the Bill and Melinda Gates Foundation will be presented along with an emerging concept involving a synthetic, oligosaccharide-based vaccine.

Drug Development for Encephalitic and Arthritogenic Infections Caused by Alphaviruses.

Ifedayo Victor Ogungbe^{a, b*}, Olawale S. Adeyinka^a, Tamia Hampton^a, Jane-Frances Chinenye Ojobor^a, Olamide Crown^a

- a. Chemistry and Biotechnology Science and Engineering Program, College of Science, The University of Alabama in Huntsville, Huntsville, Alabama 35899, USA
- b. Biomolecular Science, LLC, Huntsville, Alabama 35899, USA

Graphical Abstract



Arboviral infections, notably those caused by Venezuelan equine encephalitis virus (VEEV) and Chikungunya virus (CHIKV), continue to pose substantial public health risks, particularly in regions with limited access to antiviral therapeutics. CHIKV, originally isolated in sub-Saharan Africa, remains endemic throughout Africa and South America, contributing to recurrent and significant morbidity. The vulnerability of immunocompromised populations and the need for robust pandemic preparedness underscore the need for novel antiviral agents. Our research program employs a multidisciplinary approach to target the non-structural protein 2 (nsP2) protease, a critical enzyme in the alphavirus replication cycle. Using structure-based drug design and phenotypic screening, we have identified and optimized a series of first-in-class small-molecule inhibitors with high affinity and selectivity for the nsP2 protease. These compounds demonstrate potent antiviral activity *in vitro* and have been validated *in vivo* using murine infection models, where they significantly reduce viral titers and improve survival. Current optimization efforts are focused on enhancing oral bioavailability and blood-brain barrier permeability through medicinal chemistry and advanced formulation strategies. Preclinical studies are underway to assess in additional animal models, with the goal of advancing lead candidates toward investigational new drug (IND) studies. This presentation will detail the integrated methodologies driving our alphavirus drug discovery pipeline, highlight key structure-activity relationship (SAR) findings, and discuss the translational potential of nsP2 inhibitors.

ONE-ATOM EXCHANGE-ENABLED REVERSIBILITY OF COVALENT INHIBITION YIELDS SELECTIVITY IN CATHEPSIN S FLUORESCENT PROBES

Thales do Valle Moreira

Institut für Pharmazeutische und Biomedizinische Wissenschaften, Johannes Gutenberg University of Mainz, Germany

Abstract: Cathepsin S (CatS) is a lysosomal cysteine protease implicated in tumour progression and immune evasion via extracellular matrix remodelling, release of pro-angiogenic peptides, and invariant chain (Ii) degradation for major histocompatibility complex class II (MHCII) presentation, key processes in the tumour microenvironment (TME) [1,2]. While fluorescent activity-based probes (ABPs) are valuable tools for visualising CatS activity in live cells and tissues, existing probes (e.g., acyloxymethylketone-based BMV083 [3] or two-step vinylsulfone-ABPs [4]) rely on irreversible warheads and suffer from off-target labelling of CatB and CatL [5].

Here we report a new series of Cy5-labelled ABPs combining a peptidomimetic recognition motif (P1 = hoPhe, P2 = cyAla, P3 = pip-*N*-R) bearing either an irreversible vinylsulfonate (TVM088) or a reversible α -fluorovinylsulfonate (TVM090) warhead. The H $\rightarrow$ F substitution enables reversible covalent binding [6]. This biososteric-swap strategy has previously been shown to modulate potency and selectivity in cysteine protease inhibitors [7,8].

SDS-PAGE and Western blot analyses demonstrated that both probes bind preferentially to human rather than mouse CatS, with TVM088 yielding a stronger signal and TVM090 showing higher selectivity (less off-target labelling). Both probes bind to the ~25 kDa mature CatS, and to the ~37 kDa pro-CatS, as well as to the glycosylated forms in between (~29–30 kDa). Importantly, this binding is impaired by pre-incubation with K11777, agreeing with the active-site targeting inherited from their parent competitive inhibitors. In cellular studies using U87MG (CatS-positive) and HEK293 (CatS-negative) cell lines, TVM090 produced a fainter but more specific signal, whereas TVM088 showed more non-specific binding to proteins of similar molecular weight that do not react with anti-CatS antibody.

These results indicate that reversibility of covalent binding, achieved via the α -fluorovinylsulfonate warhead, enhances selectivity in fluorescent CatS probes. This makes TVM090 a more suitable tool for precise imaging of CatS activity in complex biological systems such as the TME. These data establish that warhead reversibility is a decisive factor for achieving high target selectivity in fluorescent probes for CatS.

References:

1. Kirschke, H. Cathepsin S. in *Handbook of Proteolytic Enzymes* 1824–1830 (Elsevier, 2013).
2. McDowell, S. H. *et al. Biochim. Biophys. Acta BBA - Mol. Cell Res.* **1867**, 118781 (2020).
3. Preya, U. H., Sayed, S., Nguyen, N. L. & Kim, J. T. P. *Exp. Eye Res.* **245**, 109981 (2024).
4. Wang, B. *et al. J. Biol. Chem.* **281**, 6020–6029 (2006).
5. Jakoš, T., Pišlar, A., Jewett, A. & Kos, J. *Front. Immunol.* **10**, (2019).
6. Schirmeister, T. *et al. Q. J. Am. Chem. Soc.* **138**, 8332–8335 (2016).
7. Fuchs, N. *et al. ChemMedChem* **18**, e202300160 (2023).
8. Müller, P. *et al. Int. J. Mol. Sci.* **24**, 7226 (2023).

Design and Synthesis of Novel AKAP-PKA-Disruptors

Niklas Ehlenz, Till Opatz

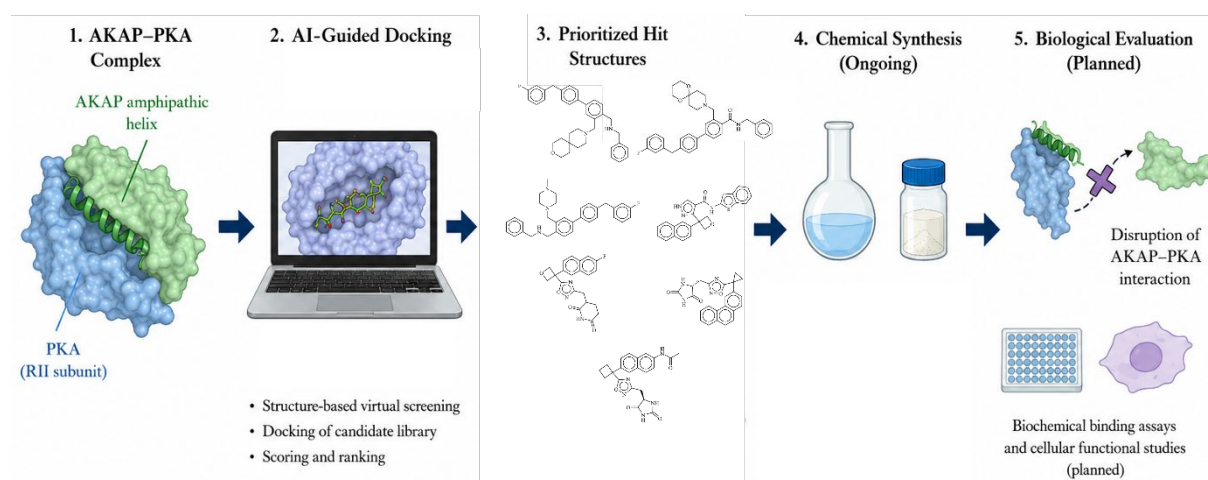
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A-kinase anchoring proteins (AKAPs) organize protein kinase A (PKA) into spatially defined signaling complexes, enabling localized and selective regulation of cellular processes. Disruption of specific AKAP–PKA interactions therefore represents a promising strategy for modulating PKA-dependent signaling with potential applications in chemical biology and drug discovery. However, developing small molecules capable of selectively interfering with protein–protein interactions remains challenging due to the high lipophilicity of the proposed binding pocket.

Herein, we describe an AI-guided structure-based approach for the identification of novel small-molecule AKAP–PKA disruptors. In cooperation with AdAtomica, AutoDock Vina was employed to explore potential ligands. From the computationally identified candidates, around ten were selected for experimental investigation.

The prioritized structures are currently being synthesized to establish an initial set of chemical probes for subsequent biological characterization. Following synthesis, the compounds will be evaluated in biochemical assays to determine their ability to interfere with AKAP–PKA complex formation. Promising candidates will subsequently be investigated in functional cellular assays to assess the biological consequences of disrupting the interaction.

This work represents an initial step toward the development of small-molecule modulators of AKAP–PKA signaling and demonstrates the application of structure-based computational design to prioritize novel chemical matter for challenging protein–protein interaction targets. The resulting compounds will provide a starting point for iterative optimization guided by experimental activity and mechanistic characterization.



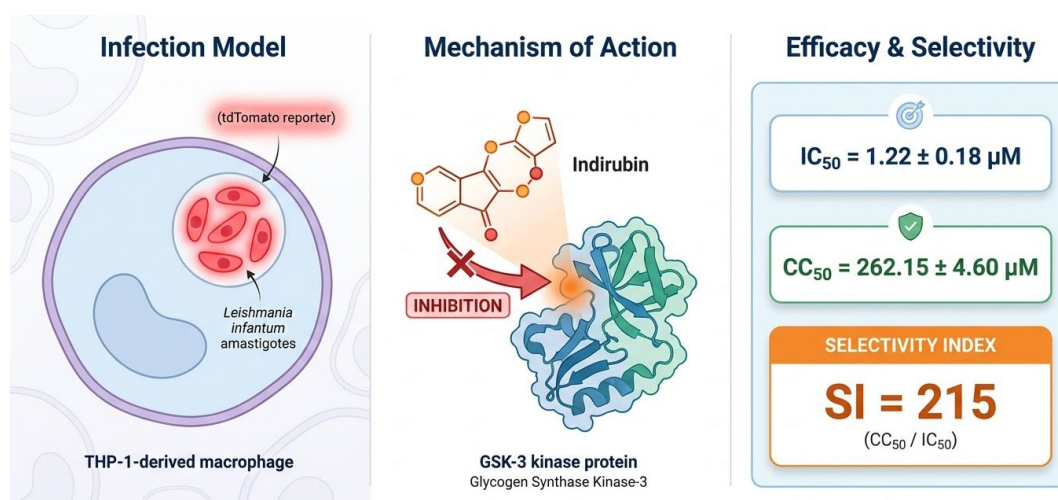
Indirubin as a promising antileishmanial agent against *Leishmania infantum* amastigotes

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Leishmaniasis are neglected tropical diseases caused by protozoa of the genus *Leishmania* and represent an important public health problem. Current treatments have limitations related to toxicity, adverse effects, prolonged administration, and the emergence of drug resistance, highlighting the need for new therapeutic agents and molecular targets. Glycogen synthase kinase-3 (GSK-3) is an essential protein in *L. infantum* and represents a potential target for the development of new drugs. Indirubin, a kinase inhibitor, targets GSK-3 and exhibits activity against *Leishmania* promastigotes. Moreover, GSK3-deleted parasites display resistance to indirubin, supporting the involvement of this kinase in its antiparasitic activity. However, its activity against intracellular amastigotes remains poorly characterized. Therefore, this study evaluated the activity of indirubin against intracellular amastigotes of *L. infantum* transfected with the *tdTomato* reporter gene. THP-1-derived macrophages were infected with *L. infantum* and treated with different concentrations of indirubin. Antiparasitic activity and cytotoxicity were assessed to determine the IC_{50} and CC_{50} values, respectively. Indirubin exhibited potent activity against intracellular amastigotes, with an IC_{50} of $1.22 \pm 0.18 \mu M$, while the CC_{50} was $262.15 \pm 4.60 \mu M$, resulting in a selectivity index of 215. These findings demonstrate the high activity and selectivity of indirubin against the clinically relevant form of *L. infantum*, reinforcing the potential of the indirubin–GSK3 interaction as a strategy for the development of new antileishmanial compounds.

GRAPHICAL ABSTRACT



The use of Glimepiride through the drug repositioning approach and its *in vitro* action against *Leishmania infantum*

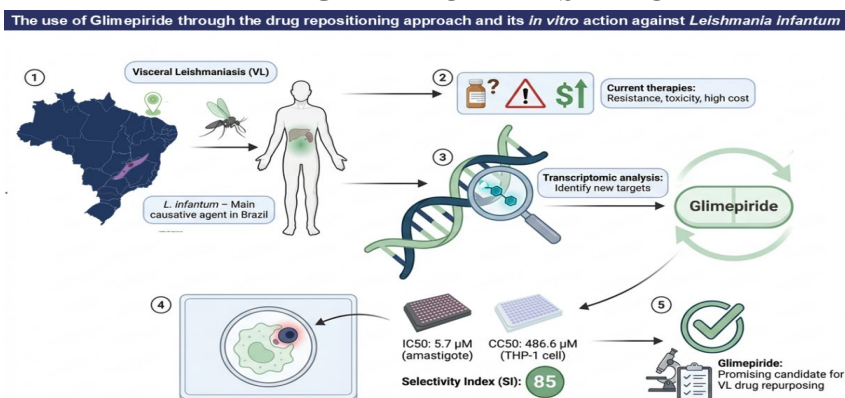
Karen Daniela da Silva Melo, Mariza Gabriela Faleiro de Moura Lodi Cruz, Daniela de Melo Resende, Silvane Maria Fonseca Murta

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DESCRIPTION

Visceral leishmaniasis are among the neglected tropical diseases of significant epidemiological impact, with visceral leishmaniasis (VL) standing out as potentially fatal when left untreated. In Brazil, where VL shows significant occurrence, the main etiological agent associated with the disease is *L. infantum*. Although treatments are available, therapeutic options present limitations related to drug resistance, toxicity, and cost, making the search for new therapeutic strategies necessary. In this context, drug repositioning is one of the methodologies with potential for identifying new therapeutic alternatives using previously approved drugs for human use. Transcriptomic analyses of differentially expressed genes in antimony-sensitive and antimony-resistant *L. infantum* strains, combined with the investigation of potential targets, identified Glimepiride as a promising compound. Glimepiride is a first-generation sulfonylurea agent used orally in the treatment of type 2 diabetes, acting to reduce blood glucose concentrations. In this study, *in vitro* assays were performed with Glimepiride to evaluate its anti-leishmanicidal action against *L. infantum* expressing the red fluorescent protein *tdTomato*. The results demonstrated that Glimepiride had an IC₅₀ of 5.7 μ M against intracellular amastigote forms and a CC₅₀ of 486.6 μ M in THP-1 cells, resulting in a selectivity index (SI) of 85. These results indicate the potential of Glimepiride as a candidate for repositioning in the treatment of VL and support the conduct of additional studies to investigate its efficacy and safety.

GRAPHICAL ABSTRACT



Antileishmanial activity of quercetin against *Leishmania infantum* amastigotes

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DESCRIPTION

Leishmaniasis are a group of neglected tropical diseases caused by protozoan parasites of the genus *Leishmania*. The parasites are transmitted by phlebotomine sand flies and can cause different clinical manifestations, including visceral and cutaneous leishmaniasis. In the absence of effective vaccines, treatment relies mainly on chemotherapy, including meglumine antimoniate (Glucantime) and amphotericin B. However, current therapies are associated with high cost, toxicity, adverse effects, and the emergence of drug-resistant parasites, highlighting the need for new therapeutic strategies. In this context, drug repurposing represents a promising approach for identifying new antileishmanial compounds. Transcriptomic analyses of two *L. infantum* lineages, one resistant and one susceptible to trivalent antimony, revealed differentially expressed genes associated with the resistant phenotype. DrugBank-based screening identified quercetin as a promising candidate. Quercetin is a flavonoid widely found in fruits, vegetables, and medicinal plants and is known for its antioxidant, anti-inflammatory, and antitumor properties. Previous studies have also demonstrated its activity against *L. major*, where it has been proposed to target quinone reductase 2, an enzyme involved in quinone metabolism. In this study, we evaluated the activity of quercetin against *L. infantum* amastigotes and its cytotoxicity toward human cells using *L. infantum* parasites expressing the *tdTomato* reporter. Quercetin exhibited an IC_{50} of $13.2 \pm 1.02 \mu M$ and a CC_{50} of $551.4 \pm 1.41 \mu M$, resulting in a selectivity index of 42. These findings demonstrate promising selective activity of quercetin against *L. infantum*, supporting further *in vivo* studies to investigate its therapeutic potential as an antileishmanial compound.

GRAPHICAL

QUERCETIN			
IC ₅₀	→	Half-maximal inhibitory concentration	→ 13.2μM
CC ₅₀	→	50% cytotoxic concentration	→ 551.4μM
SI	→	Selectivity index	→ 42

ABSTRACT

The effect of *Chromolaena hookeriana* and *Campuloclinium macrocephalum* (Asteraceae) extracts against *Trypanosoma cruzi* and *leishmania amazonensis* in vitro

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Abstract: Chagas disease (CD) and leishmaniasis are neglected tropical diseases caused by *Trypanosoma cruzi* and *Leishmania* spp., respectively. Current treatments have important limitations, including toxicity and limited efficacy, highlighting the need for new therapeutic options. Natural products are important sources of new prototypes for drug discovery, and several Asteraceae species have shown microbicidal activity. Here, we evaluated the antiparasitic activity and selectivity of extracts from two Asteraceae species, *Chromolaena hookeriana* and *Campuloclinium macrocephalum*, against trypanosomatids. Extract chemical profiles were characterized by ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS), and cytotoxicity and antiparasitic activity were evaluated against *T. cruzi* and *Leishmania amazonensis*. UHPLC-MS/MS revealed a predominance of pentacyclic triterpenoids in *C. macrocephalum*, including ursolic and oleanolic acids in the negative mode and lupeol derivatives in the positive mode. *C. macrocephalum* showed higher activity than benznidazole (Bz) against *T. cruzi* epimastigotes ($EC_{50} = 1.17$ vs. $4.47 \mu\text{g/mL}$, respectively) and was approximately nine times more potent against trypomastigotes ($EC_{50} = 0.38$ vs. $3.5 \mu\text{g/mL}$ respectively). Both extracts showed activity comparable to Bz against intracellular forms of *T. cruzi*, however, cytotoxicity also increased over time resulting in low selectivity index (≤ 8). Against *L. amazonensis* intracellular amastigotes, both extracts showed similar effect as miltefosine, with EC_{50} values ranging from 0.36 to $0.70 \mu\text{g/mL}$ and $SI \leq 16$. Overall, *C. macrocephalum* showed greater antiparasitic activity, potentially associated with its pentacyclic triterpenoid profile, supporting Asteraceae extracts as sources of bioactive compounds for developing new treatments for neglected tropical diseases.

Keywords: Chagas disease; *Trypanosoma cruzi*; Asteraceae; phenotypic screening; plant extracts.

Funding: CNPq, FAPERJ, CONICET, PROEP and Fiocruz

Antileishmanial and antimalarial activities of synthetic endoperoxide derived from marine natural products

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Malaria and leishmaniasis are both tropical parasitic diseases caused by *Plasmodium* and *Leishmania* respectively. Recent epidemiological reports revealed about 282 million cases and 610,000 deaths from malaria and about 1 million annual cases for leishmaniasis.^[1-2] Current treatments for leishmaniasis are limited to a small number of available drugs and are hindered by issues of toxicity and emerging resistance.^[3] Consequently, the development of new, nontoxic, and affordable antileishmanial agents remains a priority. Endoperoxides are effective against *Plasmodium*, as evidenced by the continual usage of artemisinins as frontline treatments for both uncomplicated and severe malaria.^[4] Plakortides and mycaperoxides are natural endoperoxides isolated from the marine sponges from the genera *Plakortis* and *Mycale*, respectively.^[5] Despite only antiplasmodial activity being reported for plakortide derivatives and a lack of studies on *Leishmania*, extracts from both sponge genera have demonstrated notable antiparasitic activity against *Plasmodium* and kinetoplastid parasites.^[6] In this project, 13 unique derivatives of these endoperoxides were evaluated for their antiplasmodial and antileishmanial activities *in vitro*. For *Plasmodium falciparum*, the drug resistant FcB1 (to CQ) strain and wild type 3D7 strain were used for *in vitro* assessments. The *in vitro* *Leishmania* assessments were performed on both axenic and intramacrophagic amastigotes of *Leishmania major*. These compounds were assessed for cytotoxicity on both human AB943 fibroblasts and murine RAW264.7 macrophages. Among the compounds evaluated, LF1440 is the most promising with SI values of >6 in *L. major*, and >85 in *P. falciparum* and should be further investigated.

References:

- [1] World Health Organization. *World Malaria Report 2023*. <https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023> (accessed December 16, 2025). p 8.
- [2] World Health Organization. *Leishmaniasis*. <https://www.who.int/news-room/fact-sheets/detail/leishmaniasis> (accessed December 16, 2025).
- [3] Domagalska M.A.; Barrett M.P.; Dujardin J.C. *Trends Parasitol.*, **2023**. 39 (4), 251–259.
- [4] World Health Organization; WHO Guidelines for Malaria. 2025 <https://www.who.int/publications/i/item/guidelines-for-malaria> (Accessed December 17th 2025).
- [5] Torres-García I.; López-Martínez J. L.; Muñoz-Dorado, M.; Rodríguez-García I.; Álvarez-Corral M. *Mar. Drugs* 2021, 19, 661.
- [6] Mostafa O.; Al-Shehri M.; Moustafa M. *Saudi J. Biol. Sci.* 2022, 29, 217–227.

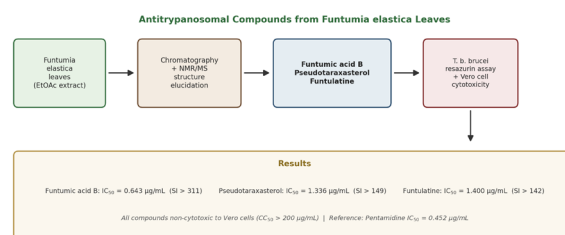
***In Vitro* Antitrypanosomal Activity of Compounds Isolated from the Leaves of *Funtumia elastica* (Preuss) (Apocynaceae)**

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GRAPHICAL ABSTRACT



ABSTRACT

Background: Human African trypanosomiasis (HAT), a neglected tropical disease caused by *Trypanosoma brucei*, remains a public health threat in sub-Saharan Africa. The current pharmacopoeia is limited by drug toxicity and emerging resistance, necessitating novel, safe therapeutic agents. *Funtumia elastica* is a medicinal plant traditionally used to treat infections. This study evaluates the *in vitro* antitrypanosomal activity and cytotoxicity of compounds isolated from its leaves.

Methods: The methanolic leaf extract was partitioned and subjected to repeated chromatography. Isolated compounds were identified using 1D- and 2D-NMR and mass spectrometry. Their activity against *T. b. brucei* was evaluated using a resazurin-based viability assay, and cytotoxicity was assessed on Vero cells to determine the selectivity index (SI). Pentamidine served as a reference.

Results: Three major compounds were isolated: funtumic acid B, pseudotaraxasterol, and the alkaloid funtulatine. All displayed potent antitrypanosomal activity. Funtumic acid B was the most active (IC₅₀ = 0.643 µg/mL), comparable to pentamidine (IC₅₀ = 0.452 µg/mL). Pseudotaraxasterol and funtulatine also showed strong inhibition (IC₅₀ = 1.336 and 1.400 µg/mL, respectively). Notably, all compounds exhibited low cytotoxicity against Vero cells (CC₅₀ > 200 µg/mL), resulting in high selectivity indices (SI > 140), with funtumic acid B demonstrating the highest selectivity (SI > 311).

Conclusion: This study identifies compounds from *F. elastica*, particularly funtumic acid B, as potent and highly selective antitrypanosomal agents. These findings underscore the plant's potential as a source of lead compounds for developing new HAT treatments and warrant further mechanistic and *in vivo* studies.

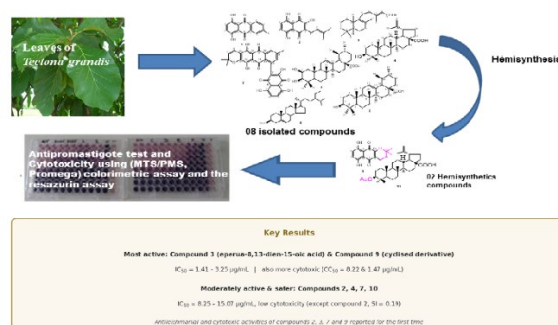
Keywords: *Funtumia elastica*; *Trypanosoma brucei brucei*; Human African trypanosomiasis; antitrypanosomal activity; natural products.

Antileishmanial and Cytotoxic Activities of Phytochemicals from the Leaves of *Tectona grandis* Linn. (Verbenaceae)

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GRAPHICAL ABSTRACT



ABSTRACT

Background: This study evaluated the antileishmanial and cytotoxic activities of the ethyl acetate extract and isolated compounds from the leaves of *Tectona grandis*, a medicinal plant traditionally used to treat malaria and parasitic infections.

Methods: Compounds were purified and isolated using chromatographic methods and identified by spectroscopic techniques. Antipromastigote activity against *Leishmania donovani* was measured using the MTS/PMS colorimetric assay, and cytotoxicity against RAW 264.7 macrophages was assessed using the resazurin assay.

Results: Eight compounds were isolated from *T. grandis*, including 5,8-dihydroxy-2-methylanthraquinone (**1**), hydroxysesamone (**2**), (+)-eperua-8,13-dien-15-oic acid (**3**), betulinic acid (**4**), ursolic acid (**5**), corosolic acid (**6**), tectograndone (**7**), and β -sitosterol glucoside (**8**). Hemisynthesis of hydroxysesamone and betulinic acid afforded two derivatives (**9** and **10**). Among six compounds screened, compounds **3** and **9** were the most active ($IC_{50} = 1.41\text{--}3.25 \mu g/mL$) but also the most cytotoxic ($CC_{50} = 8.22$ and $1.47 \mu g/mL$). Compounds **2**, **4**, **7**, and **10** showed significant antileishmanial activity ($IC_{50} = 8.25\text{--}15.07 \mu g/mL$) with low cytotoxicity, except compound **2** ($SI = 0.19$). Antileishmanial and cytotoxic activities of compounds **2**, **3**, **7**, and **9** are reported for the first time.

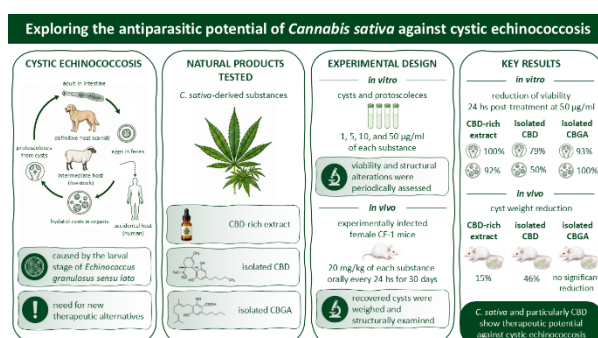
Conclusion: Hydroxysesamone, (+)-eperua-8,13-dien-15-oic acid, and betulinic acid from *T. grandis* could be represent a potential source of therapeutic candidates for leishmaniasis.

Keywords: *Tectona grandis*; hemisynthetic derivatives; antileishmanial activity; *Leishmania donovani*; cytotoxicity.

Exploring the antiparasitic potential of *Cannabis sativa* against cystic echinococcosis

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Cystic echinococcosis is a parasitic zoonosis caused by the larval stage of *Echinococcus granulosus sensu lato* (*s.l.*). Pharmacological treatment relies mainly on albendazole, although its efficacy may vary with cyst characteristics and developmental stage, highlighting the need for new therapeutic alternatives.

Cannabis sativa is an herbaceous plant that contains numerous bioactive compounds, including cannabidiol (CBD) and cannabigerolic acid (CBGA), both of which have shown antiparasitic activity against different organisms.

This study evaluated the *in vitro* and *in vivo* efficacy of a CBD-rich *C. sativa* extract, isolated CBD, and isolated CBGA against *E. granulosus s.l.*

Cysts and protoscoleces were incubated *in vitro* with 1, 5, 10, and 50 µg/ml of each tested substance. Viability and structural alterations were periodically assessed. For the preclinical efficacy study, experimentally infected female CF-1 mice received 20 mg/kg of each tested substance orally every 24 hours for 30 days. At the end of the treatment period, the cysts were recovered, weighed, and ultrastructurally examined.

After 24 hours of *in vitro* treatment at 50 µg/ml, the CBD-rich extract, isolated CBD, and isolated CBGA reduced protoscolex viability by 100%, 79%, and 93%, respectively, and cyst viability by 92%, 50%, and 100%, respectively. *In vivo*, the CBD-rich extract and isolated CBD reduced cyst weight by 15% and 46%, respectively, whereas isolated CBGA produced no significant reduction.

These findings support the potential of *C. sativa* and its bioactive compounds, particularly CBD, as promising therapeutic agents against cystic echinococcosis.

Antiprotozoal Aminosteroid Alkaloids from *Buxus obtusifolia*: Chemical Diversity, Bioactivity, and Seasonal Variation

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Human African Trypanosomiasis (HAT, sleeping sickness) and tropical Malaria remain major public health challenges in low- and middle-income countries, underscoring the need for new antiprotozoal agents. Following previous reports of antiprotozoal aminosteroid alkaloids from *Buxus sempervirens* [1] and *Pachysandra terminalis* [2], this study investigated the chemical diversity, antiprotozoal activity, and seasonal variation of aminosteroid alkaloids from *Buxus obtusifolia*, an evergreen shrub traditionally used in Kenyan folk medicine [3]. UHPLC/+ESI-QqTOF-MS/MS- and NMR-guided extraction and isolation of the dichloromethane leaf extract yielded 24 aminosteroid alkaloids, including 18 previously undescribed compounds [4]. Among these, obtusiaminocyclin was particularly notable for its unprecedented carbocyclic steroid skeleton, featuring a cyclopropane ring involving C-9, C-19, and C-11 and an unprecedented amino bridge between C-3 and C-10. All isolated compounds were evaluated *in vitro* against *Trypanosoma brucei rhodesiense* (Tbr) and *Plasmodium falciparum* (Pf), as well as for cytotoxicity against mammalian L6 cells. Deoxycyclovirobuxine-B showed the strongest activity against Tbr (IC₅₀ = 0.8 µmol/L, SI = 103), whereas 29-trimethoxybenzoyloxy cycloprotobuxoline-C exhibited the highest antiplasmodial activity (IC₅₀ = 0.5 µmol/L, SI = 12) [4]. Seasonal profiling further showed that 21 of the 24 alkaloids accumulated preferentially in the leaves, with most reaching their highest levels during the dry, warm months of January–March [5]. Overall, *B. obtusifolia* represents a rich source of structurally diverse aminosteroid alkaloids with promising antiprotozoal activity and provides useful guidance on the optimal plant material and collection period for future isolation of bioactive constituents.

References

- [1] Szabó, L, Kaiser, M, Mäser, P, Schmidt, TJ. Antiprotozoal Nor-Triterpene Alkaloids from *Buxus sempervirens* L. *Antibiotics* 2021; 10: 696. doi:10.3390/antibiotics10060696
- [2] Schäfer L, Cal M, Kaiser M, Mäser, P. Schmidt, TJ. Antiprotozoal Aminosteroids from *Pachysandra terminalis*. *Molecules* 2025; 30: 1093. doi:10.3390/molecules30051093
- [3] Beentje, H, Adamson, J, Bhanderi, D. Kenya Trees, Shrubs, and Lianas. National Museums of Kenya. 1994
- [4] Mukavi, JW, Cal, M, Kaiser, M, Mäser, P, Kimani, NM, Omosa, LK, Schmidt, TJ. Antiprotozoal Aminosteroid Alkaloids from *Buxus obtusifolia* (Mildbr.) Hutch. *Molecules* 2025 30, 4558, doi:10.3390/molecules30234558.
- [5] Mukavi JW, Sendker J, Kimani NM, Kerubo Omosa L, Schmidt TJ. Seasonal and Organ-Specific Variations of Alkaloids in *Buxus obtusifolia* (Mildbr.) Hutch: A Multivariate LC/MS Study. *Plants* 2026, 15, 1439. <https://doi.org/10.3390/plants15101439>.

Hit-to-lead optimization of benzenesulfonyl derivatives: activity as anti-*Trypanosomatidae* agents

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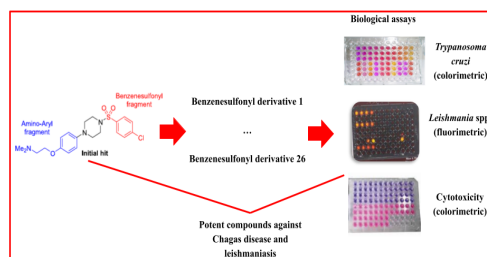
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DESCRIPTION

Leishmaniasis and Chagas disease are neglected tropical diseases caused by *Leishmania* spp. and *Trypanosoma cruzi*, respectively. Currently, there are numerous limitations associated with available treatments, such as extended treatment duration, variable efficacy, and severe side effects. In order to overcome these limitations, increasing patient adherence to treatment, the search for novel therapeutic options is urgent. This study details the early stages of hit-to-lead optimization for a benzenesulfonyl derivative, denoted as initial hit, against *Trypanosoma cruzi*, *Leishmania infantum* (causative agent of visceral leishmaniasis) and *Leishmania braziliensis* (causative agent of mucocutaneous leishmaniasis). Here, we investigated structure-activity relationships using a series of 26 newly designed derivatives, and tested their activity in biological assays against these parasites (colorimetric assay against *T. cruzi* and fluorimetric assay against *Leishmania* spp.). Results showed potential lead candidates with potent low-micromolar and sub-micromolar activities (IC_{50}) against *T. cruzi* and *Leishmania* spp., respectively, and low *in vitro* cytotoxicity (CC_{50}) against mammalian cells. The most potent compounds against *L. infantum* exhibited IC_{50} of $0.9 \pm 0.2 \mu M$ and $0.6 \pm 0.4 \mu M$ and selectivity indexes ($SI=CC_{50}/IC_{50}$) of 2,458 and 1,895, respectively. For *T. cruzi*, the most potent compound exhibited an IC_{50} of $1.7 \pm 0.1 \mu M$ and SI of 178. In conclusion, these results emphasize the relevance of this chemical class in the development of new treatments for Chagas disease and leishmaniasis.

GRAPHICAL ABSTRACT



From Molecule Selection to Clinical Phase I: A Long and Challenging Journey

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Drug development is a long, complex, costly, and uncertain journey from molecule selection to first-in-human administration. Whether the starting point is a synthetic molecule, a natural product, or a biotechnology-derived product, successful progression requires the integration of discovery, pharmacology, toxicology, pharmacokinetics, pharmaceutical development, and regulatory science. Early stages encompass target identification and validation, in silico approaches, high-throughput and/or phenotypic studies, lead identification and optimization, followed by proof-of-concept studies using increasingly predictive in vitro, ex vivo, and in vivo models. The quality and translational value of these studies depend critically on appropriate experimental design, validated models, reproducibility, adequate controls, statistical rigor, and reliable data management. Once a candidate is selected, DMPK studies characterize absorption, distribution, metabolism, and elimination and provide essential information for dose selection, exposure, formulation, and interpretation of efficacy and toxicity. These data, together with safety pharmacology and toxicology, support the critical Go/No-Go decisions. Regulatory non-clinical studies conducted according to Good Laboratory Practice are essential to establish the safety margins required for human exposure, including repeated-dose toxicity, genotoxicity, and safety pharmacology. The non-clinical package must ultimately provide a scientifically justified basis for translating animal exposure and adverse-effect thresholds, including the NOAEL, into an appropriate starting dose for clinical Phase I. Thus, reaching Phase I is not simply the completion of a checklist, but the outcome of an integrated, iterative, multidisciplinary, and internationally harmonized process. Alignment with regulatory frameworks, including ICH guidelines, is essential to ensure data quality, mutual confidence, patient safety, and efficient transition from discovery to clinical development.

Exploring Ibero-American Edible Asteraceae Species against *Trypanosoma brucei*

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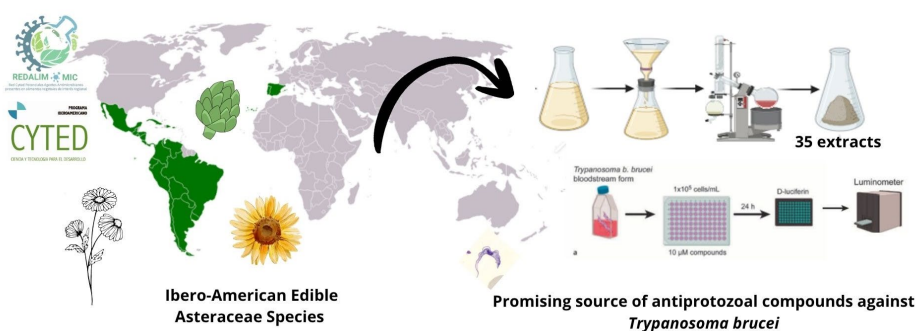
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Human African trypanosomiasis is a neglected disease caused by protozoan parasites of the *Trypanosoma brucei* complex and transmitted by infected tsetse flies. If left untreated, the disease is usually fatal. Available therapies present limitations related to toxicity, adverse effects and treatment complexity. Therefore, the identification of novel and safer antitrypanosomal agents remains a priority. In this context, edible plant biodiversity from Ibero-America represents an underexplored source of chemically diverse natural products with potential antiparasitic activity. Among these, Asteraceae is one of the largest and chemically diverse plant families. Accordingly, this study aimed to evaluate Ibero-American edible Asteraceae species for activity against *Trypanosoma b. brucei*.

As part of the CYTED REDALIM-MIC Network, “*Potential Antimicrobial Agents Present in Edible Plant Foods of Regional Interest*”, 35 extracts derived from 23 edible Asteraceae species were investigated for antitrypanosomal activity. The screening comprised 23 dichloromethane and 12 hydroalcoholic extracts. Activity was assessed *in vitro* against bloodstream forms of *Trypanosoma brucei brucei* using a bioluminescent reporter parasite cell line, while cytotoxicity was evaluated in murine J774 macrophages. Twenty-one extracts reduced parasite viability to below 50%, and ten displayed selectivity indices (SI) above 10. Dichloromethane extracts from *Baccharis latifolia*, *Artemisia absinthium*, and *Erigeron bonariensis* exhibited IC₅₀ values of 0.18, 0.25, and 0.61 µg/mL, respectively.

Overall, these results emphasize Ibero-American edible Asteraceae species as a potential source of antiprotozoal compounds. Further studies will focus on the chemical characterization of the most promising extracts by HPLC-MS to guide their subsequent bio-guided investigation.

Exploring Ibero-American Edible Asteraceae Species for Antitrypanosomal Activity against *Trypanosoma brucei*



Screening of Edible Species from Ibero-America for Antileishmanial Activity against *Leishmania panamensis*

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Leishmaniasis is a major neglected tropical disease affecting vulnerable populations worldwide, with an estimated 700,000–1 million new cases annually. Current antileishmanial treatments present important limitations, including toxicity, adverse effects, prolonged treatment regimens, and high costs. Therefore, the discovery of novel and safer antileishmanial agents remains a priority. In this context, edible plant biodiversity from Ibero-America represents an underexplored source of chemically diverse natural products with potential antiparasitic activity. The aim of this work was to evaluate the antileishmanial potential of extracts from edible plant species from Ibero-America against *Leishmania panamensis* and to identify promising candidates for natural product-based drug discovery.

Within the CYTED REDALIM-MIC Network, “*Potential Antimicrobial Agents Present in Plant Foods of Regional Interest*”, a total of 93 extracts, including 52 dichloromethane and 41 hydroalcoholic extracts, obtained from 63 edible species from Ibero-America, were evaluated *in vitro* against promastigotes of *L. panamensis*. Thirty-six extracts exhibited antileishmanial activity, with IC₅₀ values below 20 µg/mL. The dichloromethane extracts from the aerial parts of *Baccharis latifolia*, *Smallanthus sonchifolius*, *Helianthus annuus*, and *Garcinia mangostana* were among the most active and selective extracts, with IC₅₀ values of 0.88, 0.96, 1.25, and 1.32 µg/mL, respectively, and selectivity indices (SI) >10 against J774A.1 macrophages.

These findings highlight the potential of Ibero-American edible plant biodiversity as a source of antileishmanial agents and support the further chemical characterization and bio-guided investigation of the most active extracts for natural product-based drug discovery.

