Deliverable reports

Deliverables 4: Report on compounds degradability in silico pattern degradation prediction

(Action Deliverables are distinct, expected, and tangible outputs of an Action which are meaningful in terms of the Action's overall Objectives, such as reports, documents, technical diagrams, software, etc.)

Challenge of reference:

Challenge 1. Existing drugs for human and animal neglected infections against VBD are scarce, with limited efficacy and toxicity. *Therefore, a collective effort for innovative compounds and prediction tools should be identified to improve the therapeutic properties of the antiparasitic drugs and identify new drugs.*

Objective of reference (Research Coordination Objective)

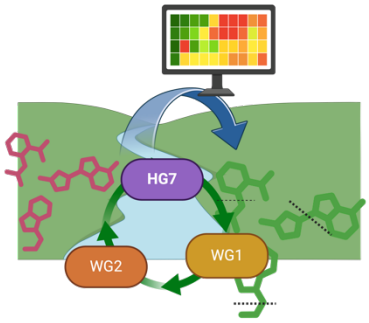
Objective 1. Coordination and integration of the medicinal chemistry programs by collecting and re-using large compounds databases available from different sources. Associate the libraries with in silico prediction of compounds behaviours (e.g. molecular and chemioinformatic properties, metabolic and chemical degradation, ADME-tox properties of metabolites) to improve the properties of the antiparasitic drugs. Actions: Increase the number of compounds to screen in a coordinated approach (from virtual or phenotypic approaches). Coordination of the compounds' libraries available and usable for screening and repurposing studies by the participants. The compounds libraries that are IP free (with no intellectual protection), discovered previously or/and during the 4 years of the Action, will be made available to all participants. Compounds degradation prediction. Collection of the information in an open access database repository dedicated to OneHealth*drug*, such as FAIRDOM database (FAIRDOM is open source database[52]). **KPI**: the Action will adopt 3 metrics to measure objective 1.1 activities to be updated, at least every 6 months 1.2 Number of compounds identified belonging to different libraries >10000. 1.3 Number of in silico studies including metabolic (enzyme assisted) and chemical degradation.

Working group of reference:

WG1. Compound libraries coordination and integration of compound design. (Challenge 1**)**
Objective: Increase the number of compounds available for the drug research projects that should be screened adopting a coordinated approach (virtually or in phenotypic approaches) to ensure innovation in anti-parasitic drug discovery. Collection and coordination of data and information about compound design.

T1.4 *Compounds biodegradability pattern prediction*. This can be performed using in silico tool that can provide insight into the chemical degradation of organic compounds under various environmental conditions. (D1.4)

Deliverable description



Biodegradability and environmental persistence of chemicals is a crucial aspect in green chemistry and sustainable drug development, serving as a key factor in evaluating the environmental fate of medicines and bioactive compounds. Compounds that exhibit poor biodegradability and high environmental persistence have the propensity to accumulate in the environment, resulting in pollution and potential harm. Therefore, it is imperative to prioritize biodegradability and strictly related properties as a critical parameter during the development of novel compounds to mitigate the environmental hazards linked to their usage and disposal. Computational modeling strategies, such as quantitative structure-activity relationship (QSAR) analysis, are crucial predictive tools for enabling the prediction of the environmental degradation potential of chemical substances, aiding in understanding their fate in the environment. QSAR can be used to predict the biodegradation potential of novel compounds by analyzing their structural characteristics. This predictive approach, rooted in green chemistry principles and sustainable pharmaceutical initiatives, facilitates the design of environmentally friendly compounds with improved biodegradability and decreased persistence. By incorporating QSAR predictions into compound prioritization strategies, scientists can focus on synthesizing molecules that exhibit enhanced biodegradation properties, thereby mitigating the environmental repercussions associated with pharmaceutical products.

Description of what we have done

Training schools

"MedChem and structural biology: tools and strategies for hit and lead optimization in the One Health perspective" Siena, Italy 27-29/09/2023 (https://onehealthdrugs.com/events/training-schools/medchem-and-structural-biology/). During this training school the importance of computational methods and tools for chemical safety and sustainability assessment, regulatory compliance, Read Across, and the applicability of in silico tools for predicting toxicity were discussed. Practical sessions using VEGA software provided hands-on experience, enabling attendees to assess chemical compound characteristics and toxicities. The event fostered networking and collaboration opportunities among participants. Overall, the significance of sustainable and innovative strategies in advancing drug development and addressing infectious diseases has been critically highlighted.

Workshops

1."**Green chemistry approaches and innovative drug delivery systems towards reducing environmental impact in antiparasitic drug discovery**" Online event, 15th March 2024 14:00-17:00. The workshop aims to explore sustainable practices that reduce the environmental impact associated with the development of antiparasitic drugs, and we invite contributions from researchers and experts within the OneHealthDrugs network. During the discussion the concept of developing predictive models able to describe the overall environmental risks to be used to facilitate regulatory decision making clearly emerged. https://www.onehealthdrugs.com/events/scientific-meeting/green-chemistry-approaches-and-innovative-drug-delivery-systems-towards-reducing-environmental-impact-in-antiparasitic-drug-discovery/

2.Workshop "**Novel leads and drugs for vector borne diseases: Targets and off targets (toxicity and ecotoxicity) and mechanism of action**" In presence event, Thursday 19th and Friday 20th September 2024, National Hellenic Research

Foundation, Athens, Greece. The workshop provided several insights on strategies and tools for sustainable drug discovery for vector borne diseases (VBDs). Biodegradability and toxicity aspects were also pinpointed with application of specific software and QSAR model for (eco)toxicity and persistence prediction. https://www.onehealthdrugs.com/events/scientific-meeting/novel-leads-and-drugs-for-vector-borne-diseases-targets-and-off-targets-toxicity-and-ecotoxicity-and-mechanism-of-action/

3.Workshop WG3, 15 May 2023 **„Ecotoxicology in drug product development and environmental impact assessment.** The One Health concept requests to consider also environmental consequences of, amongst others, a drug used to combat parasitic vector born disease. This workshop will bring together experts in the field of ecotoxicology and environmental risk assessment of chemicals in a wider sense to share their knowledge on the environmental risk assessment, procedure of pharmaceuticals, and ways to predict and text potential environmental risks of chemicals also early in the drug product development process. As this seems a field of high interest for members in this Cost Action and beyond, we hope the workshop will shed some light. (https://www.onehealthdrugs.com/events/scientific-meeting/ecotoxicology-in-drug-product-development-and-environmental-impact-assessment/)

Publications:

1. Assessing Environmental Risks during the Drug Development Process for Parasitic Vector-Borne Diseases: A Critical Reflection. Kayhan Ilbeigi, Carlos Barata, João Barbosa, Michael G. Bertram, Guy Caljon, Maria Paola Costi, Alexandra Kroll, Luigi Margiotta-Casaluci, Eli S.J. Thoré, and Mirco Bundschuh. *ACS Infectious Diseases* **2024** *10* (4), 1026-1033. DOI: 10.1021/acsinfecdis.4c00131.

Interested stakeholders

Experts in medicinal chemistry, parasitology, and environmental toxicology who focus on drug discovery. Computational chemists and biologists involved in in silico prediction modeling. Organizations seeking innovative antiparasitic compounds for drug development pipelines.Stakeholders in pharmaceutical R&D emphasizing environmentally sustainable practices. Agencies interested in setting standards and policies for sustainable drug development with low environmental impact. Researchers participating in “OneHealthdrugs” initiatives or similar global programs aiming at interdisciplinary solutions for health challenges.

Scientific impact (from the MoU)

- the engagement of novel and specific targets based on H&A biology comparative studies in particular in the field of degradome and soluble protein transporters (membrane proteins) for drug design, including specific targets against vectors;
- the discovery and optimization of high number of antiparasitic hits and lead compounds for H&A use with expected environmental low impact and higher quality profile than before;
- the development of biodegradable drug formulations with engineered targeting and engineered conjugates ensuring better *in vivo* animal efficacy.

The long-term benefits (from the MoU

- substantial improvements of the biological profile in treating parasitic diseases caused by VB parasitic diseases affecting H&A;

- engagement of RTD platforms active in the field;

Innovation

Cross-sectorial and interdisciplinary networking approach to advance the drug discovery and development field in VB parasitic diseases in H&A. Integration of the innovative approaches with the environmental impact concepts, will involve also pharmaceuticals drug discovery, manufacturing and use. The in silico degradability tools combined with experimental testing represent an essential aspect to be integrate in the early phase of drug discovery to be able to effectively help the compounds selection and potential damage prevention.