



Deliverable 5

Report on compounds synthesized (M36)

Challenge of reference:

Challenge 2. The impact of pharmaceuticals and their R&D process on the environment is high and it is responsible of huge loss due to contaminated water that affects human and animal health, generate drug resistance problems. Integrated multidisciplinary efforts (design, synthesis/extraction, in vitro and in vivo biological/animal studies, delivery) should be developed to reduce the drugs impact on the environment at every step of the drug research and development process. This requires the coordinated action of researchers and stakeholders (governmental bodies, patients' organizations, industries and SME).

Objective of reference (Research Coordination Objective)

Objective 2. Coordination of the in vitro activity of the R&D process and integration of the necessary actions for the reduction/prevention of the drugs impact on the environment. Actions: Expertise the different sources of compounds (natural source, synthetic chemistry, organic waste matter). Biological evaluation on the target and profile of the compounds in cellular assays that integrate the activities necessary for the reduction/prevention of the drugs impact on the environment. Coordinate ecotoxicology studies on selected models. HTS/MPS screening by evaluating natural source, compounds libraries, and innovative sources such as organic material of the human industrial activities. This includes hemp extraction residual waste, exhausted agricultural material, extraction from frass of insects and insects themselves, other similar waste products. Green chemistry principles approach for the compounds production, such as microwave extractions, flux chemistry. Use of predictive tools for reaction optimization and for synthesis implementation. Ecotoxicology of drugs and degradation prediction, analysis with innovative methods and analytical tools. **KPI:** the Action will adopt 3 metrics to measure objective 3 to be reviewed once a year. 3.1 Number of hits identified from the different sources compared to the compounds' library screened (many thousands available from different sources). 3.2 Number of projects developing research with organic waste material 3.3 Number of new projects planned within the One Health concept.

Working group of reference:

WG2. Integration of early phase studies and low environmental impact actions. (Challenge 2)

Objectives: Obtain new compounds from different sources and study those compound in vitro for profiling and selection for advances in the process.

T2.1 Synthesis of compounds designed using advanced medicinal chemistry strategies will be applied (diversity-oriented-synthesis library, microwave and flow chemistry other than application of the principles of green chemistry for the compounds synthesis. (D2.1)

Deliverable description.



The current therapeutic modalities for parasitic vector-borne diseases are limited and old and suffer from a variety of problems. Thus, new drugs for these diseases are urgently needed, de-risked for environmental toxicity. Novel sustainable sources of hits and leads including natural products or from valorisation of organic waste material from human activity industries may provide new drug candidates for VBDs. Novel technologies are developing continuously to recover and recycle valuable compounds and nutrients from waste materials. This new field helps in the circular economy and can contribute to the identification of novel substances for VBDs. Furthermore, green synthetic methods promote sustainability and reduce environmental impact. Integrating the green chemistry principles (such a waste reduction, use of safe solvents, energy efficient methods (microwave or ultrasound or flow synthesis) and catalysis) in drug synthesis makes it more cost-effective and environmentally responsible. These concepts and medicinal chemistry approaches are emphasized in the context of OneHealth Drugs towards the discovery and development of new drugs for VBDs.

Description of what we have done.

Training schools

“Natural products in antiparasitic drug discovery: experimental and computational approaches” 18-20/6/2024, Naples, Italy. The focus of the training school through lectures and hands-on experiments was to explore the principles underlying i) methods for isolation and structural characterization of antiparasitic metabolites from plants and marine organisms, ii) in silico methods for hit identification and optimization, and iii) green synthetic approaches for structural optimization.

“MedChem and structural biology: tools and strategies for hit and lead optimization in the One Health perspective” 27-29/09/2023, Siena, Italy 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.

“Drug discovery against parasitic vector borne diseases in-vitro assays development and screening in drug discovery”. 8-10/5/2023, Hamburg, Germany. The initial aim of drug discovery is to develop compounds that exhibit appropriate safety and efficacy profiles which can be progressed to clinical evaluation. The focus of this Training School was to explore the principles underlying target identification, biochemical and cell-based assay development, small molecule screening and in-vitro ADME-Tox profiling to produce compounds ready for clinical studies, whilst maintaining low environmental impact.

Workshops

“33rd Annual GP2A Conference, XIVth Paul Ehrlich MedChem Euro-PhD Network Meeting & COST Action One Health drugs against parasitic vector borne diseases in Europe and beyond (OneHealthdrugs)” In presence event. 11-13/6/2025, Nantes, France. In this OHD COST Action & GP2A & PaulEhrlich joint event medicinal chemistry programs were presented by young researchers and innovators promoting antiparasitic drug research while, emphasizing the concept of the environmental impact of drugs.

“Novel leads and drugs for vector borne diseases: Targets and off targets (toxicity and ecotoxicity) and mechanism of action” In presence event, 19-20/9/2024, 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.

“Green chemistry approaches and innovative drug delivery systems towards reducing environmental impact in antiparasitic drug discovery” Online event, 15/3/2024. The workshop explored sustainable practices that reduce the environmental impact focusing on green chemistry and innovative drug delivery systems and their application in antiparasitic drug discovery. 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.

"Innovative sustainable approaches in antiparasitic drug discovery: towards a one Health approach." Online event. 22/06/2023. The workshop interrogated how sustainability principles can be embedded in antiparasitic drug discovery under ongoing and future programs. Natural products, sustainable drug design, greener synthetic methods for drug synthesis, and waste valorisation strategies were discussed. Round table discussion addressed the criteria that define a drug discovery process sustainable, which steps of the drug discovery process are considered more critical for sustainability and the connection between One Health and sustainability. The workshop was inspirational and emphasized our vision for sustainability towards the future.

“Novel leads and drugs and their mechanism of action in the field of vector borne parasitic diseases” Online event. 15/5/2023. The workshop involved lectures by experts on new compounds with activity against VBDs and studies on their mechanism of actions.

STSM

- Synthesis of antimalarial 3-benzylmenadione derivatives and precursors to increase the structural diversity and decipher mode of actions - IOANNIS TOLIS (<https://www.onehealthdrugs.com/stsm/stsm-synthesis-of-the-clickable-heteroaromatic-plasmodione-analogue-it11-for-bioimaging-and-proteomics-ioannis-tolis/>)
- Libraries of analogues of Eucalyptus G-endoperoxides, antiparasite activities, mechanisms of action. Dafni Graikioti
<https://www.onehealthdrugs.com/stsm/libraries-of-analogues-of-eucalyptus-g-endoperoxides-antiparasite-activities-mechanisms-of-action/>

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 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 multitarget compounds with different profile (finalized at PROTAC and other multitarget strategy) with chimeric structures; host-parasite chimeric compounds design



- the identification of novel hits and leads from organic material from the human activity (hemp, hives, frass and others) recycling the waste from industrial production;
- improvement of procedures and use of reagents within the green chemistry field to reduce the environmental impact;

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;
- reduction, recycle and reuse of waste material with consequent long term positive environmental impact in the long term.

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. Hits and lead compounds database tailored on H&A VB parasitic diseases and obtained during the Action lifetime will foster new research activities.