

COST Action CA21111 – OneHealthdrugs

REPORT ON PROGRESS ON COMPOUNDS IN THE DISCOVERY PIPELINE

Deliverable D6

Scientific development of the OneHealthdrugs compound pipeline, 2023–2026

Executive Summary

COST Action CA21111 OneHealthdrugs has developed a multidisciplinary framework for the discovery and progression of antiparasitic compounds against vector-borne diseases of relevance to human and veterinary health. Over the course of the Action, the scientific programme has evolved from establishing common discovery resources and research connections towards an increasingly integrated pipeline in which chemical-space exploration, screening, medicinal chemistry, biological and mechanistic validation, ADME-Tox assessment, translational studies and environmental considerations can inform compound prioritisation. [1–4]

The first year, 2023, was foundational. The Action established its scientific working environment through early training schools, workshops, STSMs, surveys and scientific meetings. These activities addressed target identification, screening, hit and lead optimisation, ADME-Tox profiling, animal models, sustainable drug discovery and environmental impact. The Year 1 scientific record already contained work on antiparasitic chemical matter, nucleoside transporters, target validation, new antiparasitic scaffolds and antimalarial optimisation, demonstrating that the Action began with an active scientific base rather than starting compound discovery from zero. [5–11]

The subsequent years consolidated and expanded this foundation. In 2024, compound libraries, target-oriented discovery, phenotypic screening, medicinal chemistry and environmental integration became more strongly connected. In 2025 and 2026, the pipeline increasingly addressed advanced leads, candidate-oriented development and explicit environmental prioritisation. The OHD:LUB programme is a clear example of this maturation, linking large-scale virtual screening with structural refinement, machine-learning-based ecotoxicity filtering and experimental validation. [12–18]

The overall trajectory is therefore best described as a progression from capacity building and discovery-space coordination towards a more mature One Health pipeline in which therapeutic activity, developability and environmental performance can be considered together.

1. Purpose and Scope

This report assesses progress in compounds and compound programmes within CA21111 from the first operational year of the Action through Year 4. It focuses on scientific progression rather than on a chronological inventory of meetings. Activities such as training schools, STSMs, workshops and scientific meetings are considered insofar as they contributed to the development of the discovery pipeline, the skills and methods required to operate it, or the prioritisation of compounds.

The assessment covers 2023, 2024, 2025 and 2026, with particular attention to the transition during Years 3 and 4 from discovery and lead generation towards advanced lead development, candidate-oriented assessment and environmental integration.

2. The Discovery Pipeline and the Role of the Working Groups

The Action was structured around complementary scientific functions. WG1 focused on compound-library coordination, compound design, target selection and computational approaches. WG2 addressed early-phase studies, synthesis, screening, natural and waste-derived compounds, ADME-Tox and degradation. WG3 focused on the progression of leads and candidates from *in vitro* towards *in vivo* and translational studies. WG4 provided the environmental dimension, including ecotoxicological assessment and the integration of environmental considerations into research and development. [1]

Compound resources → Screening → Hits → Lead optimisation → Integrated profiling → Advanced leads → Candidate assessment → Translation

This framework is not a strictly linear sequence. The Action's principal added value lies in the interaction between stages: information on structure, mechanism, toxicity, pharmacology or environmental behaviour can be fed back into compound selection and optimisation.

3. Year 1 – 2023: Establishing the Discovery Framework

The first operational year established the foundations on which the later compound pipeline was built. The Action's first training school, held in Hamburg in May 2023, covered target identification, biochemical and cell-based assay development, small-molecule screening and *in-vitro* ADME-Tox profiling, with an explicit objective of producing compounds suitable for further development while maintaining low environmental impact. [6]

This was followed by the Siena training school in September 2023, dedicated to medicinal chemistry and structural biology tools and strategies for hit and lead optimisation in the One Health perspective. Together, the two schools established a direct connection between the earliest stages of discovery and the optimisation principles required for progression. [7]

The scientific programme in 2023 also began to address sustainability explicitly. The June WG2 workshop on innovative sustainable approaches in antiparasitic drug discovery brought together natural products, greener synthetic methods, waste valorisation and Safe and Sustainable by Design concepts. The discussion connected sustainability with the complete drug discovery process rather than treating it as a separate environmental topic. [8]

The Action also established an important translational bridge through the WG3 workshop on animal models for lead selection. The workshop addressed the transition from *in vitro* to *in vivo* evaluation, the 3R principles, ARRIVE reporting and new imaging technologies. This positioned preclinical evaluation within the broader One Health framework. [9]

STSM activities in 2023 provided early examples of this integrated approach. They included work on ADMET studies of antileishmanial thiazolidinone derivatives, design and biological evaluation of antileishmanial azaheterocycles targeting CK1, activity-based protein profiling of the early antimalarial lead Plasmodione, and ecotoxicological evaluation of a novel antitrypanosomal compound. [10]

The Year 1 publication portfolio also demonstrated active compound and target research. The Action's website lists 2023 scientific outputs covering nucleoside transporters as potential targets for broad-spectrum therapeutics against animal African trypanosomiasis, *Schistosoma mansoni* PDE4A target assessment, 2-aryl quinazolinone antiparasitic activity and optimisation of BIPPO analogues as antimalarials. [5]

Thus, 2023 should be regarded as the foundation year of the pipeline: it established the common language, skills, mobility mechanisms, discovery methods and initial scientific connections that enabled the more developed compound programmes of 2024–2026.

4. From Discovery Resources to an Operational Pipeline: 2024

During 2024, the Action moved from establishing the framework towards a more operational discovery environment. Compound resources and databases were developed alongside target-oriented discovery,

chemical-space exploration, screening, medicinal chemistry and mechanistic studies. The OneHealthdrugs compound database/virtual chemotheca and target database provided an organisational basis for connecting chemical matter with targets and biological information. [3,4]

The STSM programme illustrates this transition particularly well. Activities included computational discovery of calpain inhibitors, modelling of potential antiparasitic compounds, investigation of Eucalyptus-derived endoperoxide analogues, and mechanistic investigation of the H80 antileishmanial lead using MS-based omics combined with ADME/Tox/Ecotox chemoinformatics. [10]

The 2024 training programme broadened the pipeline further. Natural products were addressed through experimental and computational approaches, while cell-culture training strengthened the *in vitro* evaluation of newly developed drugs. Environmental and sustainability considerations were increasingly integrated through workshops on ecotoxicology, biodegradability, green chemistry, drug delivery and the environmental consequences of antiparasitic medicines. [11,12]

The scientific publication output reflects this broader scope. In addition to continued compound discovery and optimisation, the Action produced work explicitly addressing environmental risks during drug development and the challenges of designing environmentally biodegradable drugs. [19,20]

5. Hit Identification and Hit-to-Lead Progression

The Action combines target-based and phenotypic discovery. Target-based programmes use structural information, molecular modelling, docking and crystallography to identify and optimise inhibitors, whereas phenotypic screening provides a complementary route to active chemical matter before the molecular mechanism is fully resolved.

The Ty-Box programme illustrates the phenotypic route. High-throughput screening of 456 compounds was followed by machine-learning-supported prioritisation and synthesis of selected molecules. The study identified broad-spectrum antitrypanosomatid activity with low toxicity, and compound 40 emerged as a new lead with low-micromolar activity against *Trypanosoma brucei* and *Leishmania infantum*. [21]

The PTR1 programmes provide a complementary target-based example. Screening of a proprietary library was followed by crystallographic studies and structure-guided synthesis and optimisation. Whole-cell testing and early safety profiling then provided additional criteria for lead selection. [22,23]

These programmes demonstrate the transition from screening as an endpoint to screening as the first step of an iterative development process.

6. Representative Compound Programmes

Programme	Disease / parasite	Progression documented	Indicative stage
Ty-Box / compound 40	<i>T. brucei</i> ; <i>L. infantum</i> ; <i>T. cruzi</i>	Phenotypic screening → ML prioritisation → synthesis → antiparasitic and toxicity evaluation.	Hit → lead [21]
PTR1 inhibitor programmes	Trypanosomatids	Library screening → crystallography → structure-guided optimisation → whole-cell testing → safety profiling.	Hit → lead optimisation [22,23]
PTR1 fragment-based programme	Trypanosomatids	Fragment screening, structural analysis, fragment growth/linking and biological evaluation.	Lead development [23]
H80	<i>Leishmania spp.</i>	Imaging, proteomics and metabolomics used to investigate	Advanced lead characterisation [24]

		uptake, localisation and mechanism of action.	
Advanced lead for African trypanosomiasis	<i>T. brucei</i>	Dedicated publication on discovery and development of an advanced lead.	Advanced lead [25]
3'-Deoxytubercidin	Surra and Dourine	Reported as a potent therapeutic candidate.	Candidate-oriented [26]
Robenidine derivatives	<i>S. mansoni</i>	Derivative evaluation followed by selection of active compounds and <i>in vivo</i> assessment.	Lead evaluation
OHD:LUB	Multiple vector-borne parasites	Virtual screening → interaction-fingerprint refinement → ML ecotoxicity filtering → experimental validation.	Prioritised virtual hits [16]

7. Integrated Lead Profiling and Translational Development

As the Action progressed, compound assessment increasingly extended beyond antiparasitic potency. Selectivity, cytotoxicity, pharmacokinetic characteristics, mechanism of action, metabolism and delivery became part of the broader lead profile.

The PTR1 programmes incorporated early safety considerations, including hERG activity, CYP inhibition and mitochondrial viability. The H80 programme combined imaging, proteomics and metabolomics to establish a mechanistic basis for lead development. [22,24]

The Action also explored liposomal, polymeric and other delivery systems for antiparasitic compounds. These studies are important because they extend optimisation beyond the molecular structure of the active compound and address exposure, efficacy and tolerability at the level of the therapeutic system.

The 2023 WG3 workshop on animal models and subsequent translational activities provided an additional bridge towards *in vivo* evaluation, with explicit attention to the 3R principles and improved experimental approaches. [9]

8. Progress Towards Advanced Leads and Drug-Development Candidates

The later years provide the clearest evidence of progression towards advanced stages. In 2025, the scientific output included a dedicated study on the discovery and development of an advanced lead for African trypanosomiasis and a study reporting 3'-deoxytubercidin as a therapeutic candidate for Surra and Dourine. [25,26]

In 2026, a three-part strategic discovery roadmap explicitly addressed progression from the discovery setting through confirmed hits and from leads towards drug-development candidates. This is significant because it provides a shared framework for later-stage decision-making and clarifies the evidence expected for progression. [27]

The Action also generated exploitation-oriented outputs, including a PCT patent application related to a putative drug against leishmaniasis and/or trypanosomiasis and subsequent collaborative project development. These outputs indicate that selected scientific results have generated opportunities for continued development beyond the initial discovery activity. [6,7]

9. Environmental Integration into Compound Development

Environmental integration has evolved from a conceptual objective into an increasingly practical component of compound prioritisation. This evolution is visible from the first year, when sustainable drug discovery and ecotoxicological evaluation were already included in training and STSM activities, through the later development of predictive and computational approaches. [8,10]

The 2024 publication on environmental risks in antiparasitic drug development highlighted the limited availability of ecotoxicological data and advocated predictive tools and New Approach Methodologies at early stages of research and development. Subsequent work addressed environmentally biodegradable drugs and the environmental impacts of antiparasitic medicines. [19,20,28]

During 2025 and 2026, environmental assessment became increasingly operational through training in ecotoxicity and bioaccumulation prediction, STSM activities combining ADMET and ecotoxicology, and studies addressing biodegradability, metabolites and machine-learning-based environmental prediction. [10,29,30]

The OHD:LUB project represents the clearest implementation of this principle. More than 36,000 compounds have been screened against 22 parasitic targets. Interaction fingerprints are used to refine hits, followed by machine-learning-based ecotoxicity filtering and a Green Drug Score intended to prioritise compounds that combine antiparasitic and environmental performance before experimental validation. [16]

10. Scientific Publication Output and Pipeline Maturation

The scientific publication record provides an important longitudinal indicator of the Action's development. The Year 1 website record already documents active research in targets, transporters and new antiparasitic scaffolds. The subsequent reporting years show sustained compound discovery and optimisation alongside increasing attention to biological validation, environmental sustainability and strategic drug development. [5,31]

Year	Co-authored publications	Discovery / optimisation	Biological / mechanistic	Delivery / formulation	Environmental / sustainability
2024	51	28	2	2	2
2025	33	17	0	2	3
2026	22	11	1	2	6

The thematic groupings are used only to describe the changing scientific profile and are not official COST classifications. The publication record nevertheless supports a clear qualitative conclusion: compound discovery remained central throughout the Action, while later years show greater integration of environmental, translational and candidate-development perspectives.

11. Evolution of the Pipeline: 2023–2026

Period	Principal development	Contribution to the pipeline
2023 – Foundation	Training, STSMs, surveys and workshops established common methods and collaborations; initial scientific outputs addressed targets, screening, optimisation, ADME-Tox, animal models and sustainability.	Created the scientific and organisational infrastructure for coordinated discovery.
2024 – Operationalisation	Compound resources, target-oriented discovery, phenotypic screening, medicinal chemistry, mechanism-of-action studies and environmental assessment became more interconnected.	Moved from network formation towards an operational discovery ecosystem.

2025 – Consolidation	Advanced leads, candidate-oriented studies, ADMET/ecotoxicology activities and environmental sustainability became prominent.	Expanded the evidence base used to select and characterise promising leads.
2026 – Integration	Strategic lead-to-candidate roadmap, ecotoxicity/ML approaches, metabolites, biodegradability and OHD:LUB strengthened integrated prioritisation.	Established a clearer model for multiparametric, One Health compound selection.

12. Overall Assessment

The evidence supports a positive assessment of progress in the CA21111 compound discovery pipeline. The Action has built the components needed to move from diverse chemical space towards increasingly well-characterised and prioritised antiparasitic leads.

Pipeline dimension	Assessment
Compound resources and chemical-space expansion	Established from Year 1 and progressively expanded
Target-based and phenotypic hit generation	Well established
Hit-to-lead and medicinal-chemistry optimisation	Substantial and ongoing
Biological and mechanistic profiling	Substantial and expanding
ADME-Tox and developability assessment	Established in selected programmes and increasingly integrated
Advanced leads and candidate-oriented development	Demonstrated in selected programmes, particularly in Years 3–4
Environmental and ecotoxicological integration	Progressively strengthened from Year 1 and strongly developed in Years 3–4
Integrated One Health prioritisation	Increasingly operational, with OHD:LUB providing a concrete model

The pipeline remains heterogeneous, with programmes occupying different stages of development. This is expected for a network-level discovery programme. The principal achievement is the creation of mechanisms that allow different forms of scientific evidence to contribute to compound selection and progression.

13. Conclusions and Perspectives

The four-year development of CA21111 demonstrates a clear progression from establishment of a collaborative discovery framework towards a more mature and integrated compound pipeline. The first year was essential in creating the scientific infrastructure, common approaches and mobility mechanisms needed to connect laboratories and expertise. The following years translated this foundation into coordinated compound discovery, hit-to-lead optimisation, biological and mechanistic characterisation and, for selected programmes, advanced lead and candidate-oriented development.

A second major achievement is the progressive integration of environmental considerations. What began in 2023 as a sustainability objective and an emerging ecotoxicological research theme developed into predictive approaches, biodegradability and metabolite studies, and finally into explicit environmental filtering of virtual hits. This represents a substantive shift towards a One Health definition of compound quality.

The most valuable long-term outcome would be to consolidate the knowledge generated by the Action into a harmonised compound-level pipeline resource. Linking compound identity and source with target, parasite, development stage, biological activity, selectivity, ADME-Tox properties, mechanism of action, *in vivo* evidence and environmental characteristics would provide a durable basis for continued collaborative discovery beyond CA21111.

References

1. COST Action CA21111 OneHealthdrugs. Memorandum of Understanding and Technical Annex: One Health drugs against parasitic vector borne diseases in Europe and beyond.
2. OneHealthdrugs. Working Groups and Action structure. Official OneHealthdrugs website.
3. OneHealthdrugs. Databases list and access: OHD Target Database and OHD Compounds Database / Virtual Chemotheca. Official OneHealthdrugs website.
4. OneHealthdrugs. Working Group 4 – Integration of R&D process-environmental studies. Official OneHealthdrugs website.
5. OneHealthdrugs. Publications – Year 1 (2022–2023). Official OneHealthdrugs website.
6. OneHealthdrugs. Fraunhofer ITMP Training School, Hamburg, 8–10 May 2023: Drug discovery against parasitic vector borne diseases.
7. OneHealthdrugs. 2nd Training School, Siena, 27–29 September 2023: MedChem and structural biology – tools and strategies for hit and lead optimization in the One Health perspective.
8. OneHealthdrugs. WG2 Workshop, 22 June 2023: Innovative sustainable approaches in antiparasitic drug discovery: towards a One Health approach.
9. OneHealthdrugs. WG3 Workshop, 2023: Animal models for lead selection against vector borne parasitic diseases within the One Health concept.
10. OneHealthdrugs. STSM programme – 2023 activities, including ADMET studies, CK1 inhibitors, Plasmodione interactome and ecotoxicological evaluation.
11. OneHealthdrugs. Scientific meetings, workshops and dissemination activities, 2023.
12. OneHealthdrugs. Training schools and scientific events, 2024.
13. OHD_REPORT YEAR 2 – 2024. CA21111 Action reporting record.
14. OHD_REPORT_YEAR3. CA21111 Action reporting record.
15. OHD_REPORT_YEAR4. CA21111 Action reporting record.
16. OneHealthdrugs. Virtual screening of OHD Compound libraries against parasitic targets (OHD:LUB), 13 May 2026.
17. OneHealthdrugs. STSM programme, including ADMET/ecotoxicology and lead-characterisation activities.
18. OneHealthdrugs. Scientific meetings and workshops, 2025–2026.
19. Assessing Environmental Risks during the Drug Development Process for Parasitic Vector-Borne Diseases: A Critical Reflection. ACS Infectious Diseases, 2024. DOI: 10.1021/acsinfecdis.4c00131.
20. Development of environmentally biodegradable drugs: what are the key challenges? Expert Opinion on Drug Discovery, 2024. DOI: 10.1080/17460441.2024.2442746.
21. High-Throughput Phenotypic Screening and Machine Learning Methods Enabled the Selection of Broad-Spectrum Low-Toxicity Antitrypanosomatidic Agents. Journal of Medicinal Chemistry, 2023.
22. OneHealthdrugs scientific outputs on PTR1 inhibitor discovery and optimisation, 2024–2025.
23. OneHealthdrugs scientific outputs on fragment-based drug discovery and structural analysis of PTR1 inhibitors.
24. OneHealthdrugs scientific outputs on H80 and mechanism-of-action studies using imaging and omics.
25. Discovery and Development of an Advanced Lead for the Treatment of African Trypanosomiasis. OneHealthdrugs publication record, 2025.
26. 3'-Deoxytubercidin: A potent therapeutic candidate for the treatment of Surra and Dourine. OneHealthdrugs publication record, 2025.
27. A strategic discovery roadmap towards high-quality leads and drug development candidates for kinetoplastid diseases. OneHealthdrugs publication record, 2026.

28. Environmental impacts of drugs against parasitic vector-borne diseases and the need to integrate sustainability into their development and use. OneHealthdrugs publication record.
29. OneHealthdrugs. Training School, 2025: In silico prediction method for ecotoxicity and bioaccumulation.
30. Leveraging Ecotoxicity Parameters and Machine Learning to Rethink the Drug Discovery Pipeline. OneHealthdrugs publication record, 2026.
31. OneHealthdrugs. Publications – Years 2–4. Official OneHealthdrugs website.