The workshop, titled

"Integration of Green and Greener Actions into Medicinal Chemistry Programmes,"

I. Introduction and Opening Remarks

Biljana Arsić (University of Niš) opened the session as a leader of Working Group 4. She welcomed participants and outlined the workshop's goal: exploring sustainable strategies in drug discovery and development.

The sessions were categorized into four main pillars:

Green Frontiers in Medicinal Chemistry: Sustainable strategies in drug discovery.

From Molecule to Medicine: Translating molecular insights into therapeutic potential through property prediction.

OneHealthDrugs: A holistic approach bridging human medicine, animal health, and the environment.

Omics Data to Drug Breakthroughs: Utilizing complex biological data for next-generation medicines.

Maria Paola COSTI (Chair of the COST Action) provided welcoming remarks despite minor technical connectivity issues at the start.

II.

Presentation 1: New Heterocyclic Phosphomimetic Derivatives

Presenter: Theodora Kalogeropoulou (National Hellenic Research Foundation)

Research Context: Neglected Tropical Diseases (NTDs). Theodora focused on Leishmaniasis, a vector-borne disease endemic to 98 tropical regions, causing approximately 40,000 deaths annually. Current treatments (antimonials, Miltefosine) face issues with toxicity, high cost, and rising clinical resistance.

Design and Green Strategy

The Problem: Miltefosine's toxicity is attributed to its long aliphatic chain and teratogenic nature. The Solution: Applying bioisosterism to replace the phosphate group with 4-thiazolidinone, a privileged heterocycle. Green Chemistry: Utilized a three-component, one-pot multi-component reaction (MCR) involving an aldehyde, an amine, and methyl thioglycolate. This approach is considered sustainable due to its high atom economy and reduced processing steps. Findings and In Vivo Results: The cyclopentadecyl ring (15-carbon carbocyclic moiety) proved most effective, balancing efficacy and reduced toxicity.

Pharmacokinetics (PK): Snapshot studies after oral administration (20 mg/kg) showed quick absorption. However, despite favorable in vitro data, in vivo efficacy was limited.

Future Directions: The team is investigating whether the compounds reach target organs (liver and spleen) and considering twice-daily administration to counteract short half-lives.

III. Presentation 2: Integrating Green Chemistry in the Synthesis of Bioactive Chalcones

Presenter: Sandra Gemma (University of Siena)

Focus: Oxyprenylated Chalcones

Chalcones are natural precursors to flavones with significant anti-inflammatory and antimicrobial properties. Sandra's team aimed to improve their affinity for bacterial and parasitic membranes by decorating the scaffold with protonatable chains.

Methodology: Design of Experiments (DoE). Sandra highlighted the shift from "One Variable at a Time" (OVAT) optimization to Design of Experiments (DoE). DoE Benefits: A statistical approach that allows the variation of multiple factors simultaneously to find true optimal conditions with minimal experiments. Green Application: By optimizing the Claisen-Schmidt condensation, the team replaced THF with 2-Methyl-THF (a greener alternative) and optimized base equivalents and reaction time. Results: Yields increased from an initial 12% to 64% (and up to 90% for specific derivatives) through DoE optimization.

Discussion Summary. Participants discussed the scalability of DoE and the potential for miniaturized organic synthesis using 24-well plates and mass spectrometry (MS) to further reduce chemical waste.

IV. Presentation 3: OneHealthDrugs and Regulatory Updates

Presenter: Maria Paola COSTI (University of Modena and Reggio Emilia)

The Regulatory Landscape

Maria Paola emphasized that early-phase drug discovery must include ecotoxicological (EcoTox) evaluation. She noted that as of 2022, planetary boundaries for novel chemical entities have been exceeded, making it impossible to detect every individual entity in the environment. COST Action Achievements: Implementation of EcoTox assays in collaboration with laboratories like Fraunhofer (Hamburg). Development of an EcoTox algorithm to help score and rank compounds based on environmental profiles during virtual screening.

Maintenance of a database containing 12,000 compounds with toxicity and EcoTox data.

Policy and Future Goals. The project aims to release a Position Paper (July 10, 2026) and a Policy Brief (September 2026) to influence regulatory bodies (like the EMA) regarding Environmental Risk Assessment (ERA) for both human and veterinary medicines.

V. Presentation 4: Rethinking Antiparasitic Drug Discovery

Presenter: Biljana Arsić (University of Niš)

Ribosomal Modeling for Malaria

Biljana discussed the challenge of isolating the apicoplast (a unique organelle in Plasmodium) from mitochondria. In Silico Approach: Her team constructed a model of the apicoplast ribosomal exit tunnel using ab initio molecular modeling (I-TASSER).

Validation: They docked macrolide antibiotics (Erythromycin B derivatives) into this model. The docking scores correlated with experimental IC50 values, confirming the model's reliability as a prediction tool.

Drug Repurposing for Leishmaniasis (Kala Azar). Using the Drugs4All platform and the Electron-Ion Interaction Potential (EIIP) descriptor, the team identified existing drugs for

potential repurposing: Nifuroxazide: An anti-diarrheal drug showing promising in vitro results from previous literature. Entecavir: A Hepatitis B medication identified via molecular docking against the RAP5A protein. Amlodipine: Identified as a promising candidate through network-based pharmacology.

VI. Conclusion and Closing. The workshop concluded with a call for continued collaboration ("acting like social bees") to maximize the impact of the COST Action. The participants were encouraged to integrate ecotoxicology into their ongoing medicinal chemistry projects and to attend the upcoming meeting in Brussels in July 2026.