Natural products in antiparasitic drug discovery: experimental and computational approaches

Tuesday 18 June – Thursday 20 June 2024

University of Naples "Federico II", Italy

Students' collaborative report

Day One Report

Professors Orazio Taglialatela-Scafati, Marialuisa Menna, and Caterina Fattorusso began the opening greetings by warmly welcoming all participants. They proceeded to present the school's objectives. They emphasized the importance of studying natural products as an inexhaustible source of new compounds to be used in the treatment of parasitic diseases.

Prof. Donatella Taramelli's introductory lecture provided us important insights for understanding the process of "Drug Discovery against parasitic diseases in One Health perspective". Tools for malaria prevention, control and elimination were presented.

The second lecture, led by Dr. Carmina Sirignano, entitled "Bioprospecting of plant-based natural products: current perspectives and future insights", aimed to show us the approaches and techniques used in the study of medicinal plants to isolate and characterize new bioactive metabolites. Several case studies were presented. Additionally, an overview of how new advances in bioinformatics tools and analytical chemistry techniques have recently enhanced the field of natural products research was provided.

The afternoon session was opened by Dr. Marcello Casertano who held his lecture entitled "Diversity-oriented synthesis: a tool for the identification of novel active small molecules for challenging biological targets". This lecture described the application and the goals of diversity-oriented synthesis approach which is a currently performed approach for generation of structurally diverse small molecules collection. Selected case studies were presented showing how it is possible to explore the biological relevant chemical space of small molecules

for discovery of novel antiparasitic agents.

The afternoon session continued with the lecture of Prof. Caterina Fattorusso entitled "Computational approaches in natural product drug discovery: deciphering the code". This lecture gave us an overview of the application of computational tools in support of the natural product drug discovery process. In particular, this lecture provided us the general principles of the ligand-based and receptor-based computational approaches. Additionally, the computational methods used in these approaches, their applications and their aims were presented.

The afternoon session finished with the lecture of Prof. Marco Persico entitled "Design of Nature inspired antiparasitic drugs: applications" aimed to show us two examples of computational applications. In particular, this lecture showed us, as first example, a ligand-based approach aimed to design new redox active anti-parasites starting from two different natural scaffolds and, as second example, a target-based approach aimed to design new covalent enzyme inhibitors. Additionally, an overview of the computational techniques used in these applications was provided.

Day Two Report

09:00h – 13:00h Laboratory Learning Activities: Bioprospecting and DOS.

In the morning session, we went to the Chemistry Laboratories where we were divided into four groups of four. Concetta Imperatore, Marcello Casertano and Carmina Sirignano led the practical lesson which in the first part was addressed to better understand all the steps involved in isolating a natural product from a crude extract. The functioning and importance of instruments such as MPLC and HPLC in the purification process were described, followed by the analysis of an LC-MS profile of an extract through molecular networking. It was highlighted how this approach is particularly useful in the fields of natural product research, as it allows us to systematically explore complex datasets and uncover new chemical entities based on their structural relationship. The second part of the session regarded the oxidation of the 2-benzyl-1,4-dimethoxybenzene via addition of cerium ammonium nitrate as representative example for synthesis of quinone-derived compounds. TLC was used to monitor the reaction before performing liquid-liquid extraction and 1H NMR analysis of the crude material.

14:00h – 18:00h Practical Work, Demonstrations & Task-based Group Activities: ligand-based and receptor-based computational techniques in natural product drug discovery.

In the afternoon session, we went to the Computer Laboratory. Caterina Fattorusso, Marco Persico and Oleh Tkachuk led a practical session, where they showed us the use of BIOVIA Discovery Studio software.
In the first part, we learned to import the structures of small ligands by using the SMILES code and then to parameterize the imported structures by using a forcefield. Then, we learned to create a 3D pharmacophore model adding the pharmacophoric features and the location constraints. Finally, we learned to use the created 3D pharmacophore model to perform a 3D-database searching. In the second part, we learned to download a protein structure from the Protein Data Bank (PDB), to open the structure in the software and to parametrize it. Then, we learned to create a structure-based pharmacophore by using the downloaded protein and then, to use it to perform a 3D-database searching.
In summary, firstly we were trained on how to create a 3D pharmacophore model using a small natural compound or using a protein structure. Secondly, we were trained to use the created 3D pharmacophore models to perform a search in different 3D database to identify new hit compounds.
Finally, we were divided into four groups, and we tried to reproduce the learned procedures selecting one of the three structures prepared by trainers. We presented and discussed the results of this group activity in the third day of the training school.

Day Three Report

The last day of the Training School was opened by the lecture of Prof. Gabriele Cruciani entitled "In silico methods for hit identification and optimization" which gave us an overview on computational tools for hit identification and optimization.

Then, Dr. Sheraz Gul presented his lecture "Biological properties of Hit, Lead and Candidate molecules" based on the High throughput screening (HTS) for rapidly test a large number of samples for their biological activity.

The session continued with the flash-presentations of the Selected Training School attendees on their research interests in natural product drug discovery. Each presentation was followed by Q&A which fostered the deepening of certain themes and the exchange of contacts between participants.

Then, we were involved into the "Challenge-Based Learning" session by presenting the results of the group activities. Each group was involved in solving the challenges proposed by the trainers during the practical work of the second day. The challenges were based on the structure elucidation (1H and MS spectra) of natural products, suggest a method of synthesizing products/intermediates from a common starting material and their purification conditions. Additionally, we were invited to present and to discuss the results of our computational group activity.

Finally, Prof. Maria Paola Costi held the closing remarks on the Training School and the potential opportunities of the Cost Action CA21111 OneHealthdrugs network.