GROUPS EXPERTISE

Professor Bruno Botta’s Unit has expertise in developing chemical libraries of novel bioactive compounds (variably substituted flavonoids, benzophenones, xanthones, anthraquinones, alkaloids, steroids, terpenoids), many identified from natural extracts obtained from medicinal plants. The Unit can provide expertise with a unique in‐house library of about one thousands of bioactive natural compounds, mostly isolated from several plants used in traditional medicine of South America and collected over the years, and available at the Organic Chemistry Laboratory of the Department of Chemistry and Technology of Drugs (Sapienza University of Rome, Italy). This library consists of natural products belonging to different classes of organic compounds which were previously published and fully characterized. The 70% of them were isolated only by this research group and most plants are indigenous only to biodiversity-rich countries especially of the tropics and subtropics. Therefore, the library is a unique and diverse collection of natural products. It exhibits a wide range of pharmacophores, a high degree of stereochemistry and a large range of molecular weights: these properties contribute to the ability of the collection to provide hits. It was then enlarged by the addition of other natural small molecules from commercially available sources and synthetic or semi‐synthetic derivatives. Currently, all components of our collection are incorporated into a virtual library, and their chemical and physicochemical features are analyzed by means of cheminformatics tools, showing a satisfactory chemical diversity. Therefore, this in-house library offers a unique chance to identify unexpected new scaffolds for the development of therapeutically-relevant molecules. Furthermore, it is still successfully screened *in silico* and *in vitro* for the identification of hit and lead compounds in previous early-stage drug discovery projects.

Botta’s group will be able to develop structure-based and ligand-based drug design approaches for selecting a limited number of candidate molecules likely to be active against a chosen biological receptor. It is also important to consider that structure-based drug design directs the discovery of a drug lead, which is not a drug product but, specifically, a compound with at least micromolar affinity for a target. Ligand-based computational methodologies must be applied when the three dimensional coordinates of the target macromolecules are unknown. In particular, these approaches allowed to generate theoretical models able to rationalize at a quantitative level the relationships between the compounds structure and their experimentally tested activities, withdrawn from published literature. Structure-activity relationships (SAR) and quantitative SAR (QSAR), as well as three-dimensional QSAR analyses generate theoretical model for this purpose, also including molecular descriptors profiling compounds from the AMDE-Tox point of view. Moreover, different programs have been applied to build pharmacophoric models starting from a set of compounds and their activities. These approaches were used to discover small molecule targeting selectively the Hedgehog pathway hyperactivated in cancer stem cells leading to the identification of a natural isoflavone actually at the end of the preclinical phase.

In order to concentrate experimental efforts on a relatively low number of molecules, and to explore as much as possible the chemical and scaffold space of the library, Botta’s group employed a cheminformatics approach, when structure-based and ligand-based drug design approaches cannot be performed. To this end, a diversity-oriented random selection (DORS) of compounds was performed by means of a clustering algorithm, which is based on a combination of fingerprints and common substructure. Therefore, the library was clustered based on fingerprints and substructure search allowing to test in vitro a representative subset of molecules.

In addition, Professor Bruno Botta’s Unit has expertise in another important phase of drug discovery: optimizing active Hits up to Lead compounds or, at least, Lead candidates by improving potency, stability, physicochemical features (i.e. water solubility, logP, polar surface area PSA, etc…), chemical properties, and metabolic/pharmacokinetics parameters.

In the last ten years, combining computational modeling, organic synthesis, and biological evaluations in a concerted multidisciplinary strategy, the library provided the leads for compound that are currently under patent, especially as anticancer and antimicrobial agents. (brevetti)

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