Design and synthesis of nature-inspired compounds as potential anti-inflammatory/anticancer agents

Natural products (NPs) are a privileged class of compounds with high diversity and suitable for inspiring new rationally designed multi-target drugs [1, 2]. Indeed, the research of natural compounds relies on a wide variety of lead structures, which may be used as templates for the development of new potential drugs. As a matter of example, recent studies concerning the pharmacological applications of nature-derived secondary metabolites disclosed the possible application of tanshinones against inflammation, especially in neurodegenerative pathologies like Parkinson's or Alzheimer's diseases [3, 4] and of marine peptide petrocidine as possible anticancer agent [5].

The proposed PhD project has a multidisciplinary structure including all the steps of drug discovery: design, total synthesis, SAR studies, investigation of ligand/enzyme molecular interaction, and pharmacological *in vitro* evaluation in the aim to develop derivatives with optimized potency/selectivity towards specific targets in the inflammatory/cancer field. The so far scarcely investigated epigenetic modulator BRD9 (bromodomain containing 9) [6] and some downstream enzymes of the arachidonic acid cascade, such as mPGES-1 (microsomal prostaglandin E synthase-1) [7] and sEH (soluble epoxide hydrolase) [8], will be the privileged protein targets of our investigation. Focused libraries of close structural analogues of selected NPs will be tailored thanks to the collaboration with external partners; virtual combinatorial libraries will be then synthetized using optimized synthetic procedures, considering commercially available building blocks, taking in account the innovative and leading-edge technologies and, when possible, fast, sustainable and eco-friendly synthesis methodologies. In this frame, viridicatin, petrocidin and tanshinone, will be considered as starting chemical items due to their interesting pharmacological properties and the possibility of being chemically modified. The most promising synthetized compounds will be further optimized evaluating the ADME properties and subjected to deeper pharmacological investigation.

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