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PROJECT TITLE
Exploration of the antidiabetic and anti-inflammatory chemical space *via* marine natural products by Diversity Oriented Synthesis (DOS) and/or Fragment-Based Ligand Drug Discovery (FBLDD) approaches

Project description
Bioactive natural products can be envisaged as biologically validated starting points for the discovery of ligands capable of acting on pharmacological targets in a specific and selective manner to achieve a therapeutic effect.[1] The aim of this research proposal is to exploit the chemical diversity associated with marine natural products to identify innovative leads (i.e. with a different structure from known drugs active on the same target or active on a new target) capable of counteracting the development and complications of the metabolic syndrome and diabetes, in particular insulin resistance, obesity and inflammation. In this scenario, complex and unusual natural structures of marine origin, particularly those produced by sessile invertebrates,[2] may represent a valuable resource of chemical and biological novelty,[3-7] especially when used in combination with organic synthesis approaches such as Diversity Oriented Synthesis (DOS) and/or Fragment-Based Ligand Drug Discovery (FBLDD). [8, 9]
The research proposal has three main lines: 1) discovery of new chemical diversity through chemical investigation of marine organisms; 2) enlargement of chemo-diversity through synthesis of modified derivatives of natural hits (DOS); 3) creation of chemical libraries of synthetic fragments that retain only parts of the original structure of the natural hit (FBLDD). The molecules generated through the three approaches will be exploited by screening several emerging pharmacological targets for the development of new anti-diabetic and anti-inflammatory drugs, such as protein tyrosine phosphatase 1B (PTP1B), aldose reductase (AKR1B1), carbonic anhydrase and human 15-lipoxygenase-1 (15-LOX-1) This part of the project is being carried out through already existing collaborations with Italian and foreign researchers studying the characteristics and activities of these enzymes. The ultimate goal of the research is the discovery and initial optimisation of new leads with anti-diabetic and anti-inflammatory potential and, above all, of multiple ligands capable of overcoming the drawbacks of polypharmacology.

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