Title: Development of small molecule modulators of epigenetic targets

Epigenetics plays a pivotal role in tissue- and cell type-specific gene expression via diverse molecular modifications to both DNA and chromatin; alterations in epigenetic landscapes are hallmarks of many complex human diseases. Increasing evidence points to unveiling a new guise for epigenetic targets as key players in many non-oncological diseases, in particular rare diseases (eg. cystic fibrosis, idiopathic pulmonary fibrosis and retinopathies) and disorders involving neural plasticity, including neuropathic pain.

The aim of the present PhD project will be the development of modulators of epigenetic targets, with a special focus on enzymes responsible for DNA methylation and methylation/acetylation of histone and non-histone proteins (eg. histone deacetylases, METTL3 and G9a methyltransferases).

The PhD project will rely upon the strong background of the research group in the development of extremely potent and selective chemical probes for a variety of epigenetic targets. The PhD activity will be devoted to compound optimization as well as the identification novel prototypes to be subsequently embarked in hit-to-lead transition. The increasingly appearing structural information on epigenetic targets and their X-ray structures in complex with several modulators will allow more effective structure-based design strategies, thus driving the drug discovery trajectory toward potent, selective and safer compounds, to be employed as novel therapeutic options in several disease states. A particular focus will be devoted to the assessment and optimization of ADME + T properties for the most promising chemical entities, that will be finally engaged in *in vitro* and *in vivo* proof-of-concept studies on relevant disease models, through both industrial and academic collaborations. For the exploration of a wider chemical space towards novel epigenetic modulators, suitable enabling technologies will be employed to improve synthetic efficiency and industrial scalability, while reducing environmental impact whenever possible.