ABSTRACT

A large amount of evidences indicate that dysregulation of protein methylation is linked to the genesis and progression of several human diseases, including cancer. Therefore over the past years small-molecule modulators targeting Protein Methyltransferases (PMTs) have been actively developed as anticancer drugs as well as chemical tools to better understand the biological and physiological roles of protein methylation. In this thesis the design, synthesis and biological evaluation of three different classes of compounds, designed as isozyme-selective PRMT inhibitors, are reported. (1) Inspired by the structure-activity relationships (SAR) of pyrazole and indole compounds, the most potent PRMT4 inhibitors, we developed a series of pyrrole-based compounds, designed as inhibitors of PRMT4. A potent inhibition was observed when testing pyrrole derivatives against PRMT4 (i.e. **EML 438**, IC_{50} = 2.42 μM), nevertheless they didn't prove a significant cellular activity, due to their poor transcellular permeability. Therefore, in order to increase the activity and the lipophilicity of these compounds and supported by computational studies, we started a process of structural optimization of this class of compounds. Novel derivatives have been designed and selected. (2) Furthermore, in collaboration with Professor Nathaniel Martin from the University of Utrecht, we have successfully synthesized a set of novel PRMT4 bisubstrate inhibitors. Preliminary screening of their biological activity revealed a nanomolar inhibition of PRMT4 (**P2-C3-unsat**, IC_{50} = 43 nM) with about 900-fold selectivity for CARM1 over PRMT1. This data confirm our hypothesis that a potent and selective enzymatic inhibition is achieved by compounds characterized by structural features able to bind both the enzymatic substrate binding sites, thereby mimicking the transition state. (3) We also started a program aiming at developing inhibitors of PRMT3. Three series of indole-based compounds were prepared and their activity against a panel of PRMTs was assessed. **EML598** and **EML599** showed a selective inhibition of PRMT3 at fixed dose (70% at 100 μM). Further biophysical assays are still ongoing in order to better evaluate their biological activity.