ABSTRACT

The methylation of arginine residues is a common post-translational modification, performed by a family of nine methyltransferases known as PRMTs (Protein Arginine Methyltransferases). Arginine methylation plays a key role in gene regulation due to the ability of the PRMTs to deposit activating or repressive "histone marks". These modifications correlates PRMTs to several biological processes and their aberrant activity is involved in many pathological conditions like inflammation, neurodegeneration, and cancer. Therefore, PRMTs have been identified as promising therapeutic targets. This Ph. D. project is focused on the design, synthesis and *in vitro* evaluation of new putative modulators of PRMTs. To this purpose, different medicinal approaches have been applied to obtain different classes of compounds. The main strategy exploited a deconstruction–reconstruction and fragment growing approach, starting from naphtalene-based type I PRMT inhibitors, previously identified by us. Herein we report the identification of **EML981,** whose inhibitory activity toward PRMT4 has been supported by biochemical and crystal structure studies. Subsequently, the lower homologous **EML734** has been identified as the first in class dual inhibitor of PRMT7 and PRMT9. Moreover, at the University of Vienna, I have been implicated in the development of a new synthetic methodology defined as "Alkene 1,3-Functionalization". This procedure has been applied to develop analogues of **EML981** bearing of sp3-rich fragments with a view to strengthen the intermolecular interactions with protein target and to increase the *druglikeness* of compound. Concurrently, three side approaches have been investigated. The first reports the pro-drug strategy, applied to promising pyrrole-based compounds previously identified by us. The second approach involves the design, synthesis and biological evaluation of compounds able to induce protein degradation (PROTACs). Finally, the scaffold replacement approach has been applied to inhibitor **EPZ007345,** affording a small library of compounds.