ABSTRACT

The inactivation of tumor suppressor genes, which often results from epigenetic silencing associated with DNA hypermethylation, plays a pivotal role in the development of most forms of human cancer. Moreover, there are several reports demonstrating a strictly link between DNMT1 disregulation and oncogenensis. Nucleoside analogues effectively inhibit the activity of DNA methyltransferases, but their high cytotoxicity make the development of non-nucleoside inhibitors highly desirable. Procaine and procainamide exhibit a weak DNA demethylating activity and are "repositionable" as non-nucleoside inhibitors. In this thesis, two series of Δ^2-isoxazoline constrained analogues of procaine/procainamide are prepared and their inhibitory activity against DNMT1 is tested. Among them, **5b** is far more potent *in vitro* (IC_{50} = 150 μM) than other inhibitors and exhibits a dose-dependent antiproliferative effect against HCT116 human colon carcinoma cells. On the basis of competition assays, we assesse that **5b** competes with the cofactor and propose it as a novel lead compound for the development of new, longer compounds, obtained by the combination of this SAM-competitive scaffold with "warheads" targeting the nucleotide binding site, as "bisubstrate" inhibitors of DNMT1.

Moreover, starting from a virtual screening approach, the synthesis of the six top scoring compounds, obtained by the analysis of the NCI database, is reported. Among them, NSC140052 results the most powerful compound of this series, becoming the starting point for the synthesis of a small library of new compounds.

Finally, a scalable two-step continuous flow synthesis of nabumetone and relate 4-aryl-2-butanones has been developed. As demonstrated for the synthesis of 4-(4-methoxyphenyl)-3-buten-2-one (**52b**), a throughput of 0.35 kg product per hour can easily be obtained using this technique.