Synthesis of small molecules as potential DNA methylation modulators

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Epigenetic modifications play an essential role in the establishment and regulation of cellular differentiation and gene expression.[1] In eukaryotes, DNA methylation is the most stable epigenetic mark.[2] DNA methylation occurs at C5 position of the cytosine ring in CpG island often located in gene regulatory regions (i.e. promoters)[3] through the action of three active DNA methyltransferases (DNMTs): DNMT1, DNMT3A and DNMT3B. These enzymes catalyze the transfer of a methyl group from *S*-adenosyl-*L*-methionine (SAM) to the C5-cytosine.[4]

A number of DNMT inhibitors have been developed to date. They can be classified into two general categories: nucleoside and non-nucleoside DNMT inhibitors. Nucleoside inhibitors after incorporation in the DNA structure cause covalent trapping and subsequent depletion of DNA methyltransferases.[5] Moreover these molecules are characterized by cellular and clinical toxicity, which led to the search of new and more specific drugs. Non-nucleoside DNMTs inhibitors, are represented by a heterogeneous class of compounds which can directly inhibit the enzyme. Different compounds have been identified from natural products and medicinal chemistry modification of established drugs or thanks to synthetic and virtual screening efforts (i.e. RG 108, SGI 1027, NSC 14778, NSC 319745 and their analogues).[6]

So far the relatively poor inhibitory activities toward DNMTs, the lack of isoform selectivity coupled with significant cytotoxicity, hampered their therapeutic development; therefore, new potent and highly selective DNMT inhibitors are urgently needed. In this work we studied the development of small molecules DNMT inhibitors obtained by modulation of NSC 137546 scaffold. The structure of NSC 137546 can be formally dissected into three molecular moieties: the substituted aromatic ring (A), the amide linker (B), and the terminal aminoacidic portion (C) (Figure 1). All the three molecular moieties were modulated in order to improve DNMT1 inhibition while maintaining selectivity *vs* DNMT3B and to study the unreported effect on DNMT3A activity.

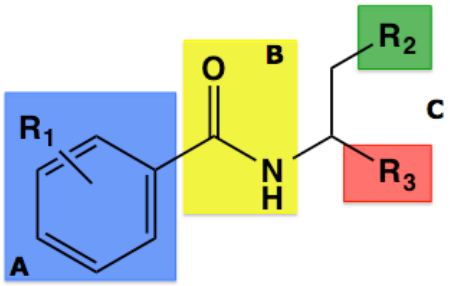

Figure 1. Modulation of NSC 137546 scaffold.

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