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Antiproliferative and Apoptotic Activities of Sequence-Specific Histone Acetyltransferase Inhibitors

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ABSTRACT

In parallel to monomeric epigenetic regulators, sequence-specific epigenetic regulators represent versatile synthetic dual-target ligands that achieve regulatory control over multi-gene networks. Development of DNA-binding domain (DBD)-HDAC inhibitors and DBD-HAT activators, which result in increased histone acetylation, has become one promising research field. However, there is no report regarding the gene regulatory pattern by sequence-specific epigenetic repressor. We report here for the first time, the synthesis of DBD-HAT inhibitors and demonstrate that these conjugates could retain their dual-target activity using predicted working model of thermal stability assay and *in vitro* HAT activity assay. Evaluation of antiproliferative activity in cancer cells showed that **2** (with a medium linker length of 13-atom) exhibited the highest antiproliferative activity in p53 wild-type cancer cell lines (IC₅₀ of 1.8-2.6 μM in A549 and MV4-11 cells) and not in p53 mutant cancer cell lines. A mechanistic investigation using microarray analysis and an apoptotic assay showed that the antiproliferative effect of **2** occurred *via* the up-regulation of p53 target genes, and the subsequent initiation of p53-dependent apoptosis. Our research on sequence-specific dual-target epigenetic repressor offers us an alternative way to modulate HAT-governed therapeutically important genes and contributes to offer a fresh insight into antitumor therapeutics.

Keywords:

Epigenetics; Sequence specificity; Polyamide; HAT inhibitor; Antiproliferation; Apoptosis

Abbreviations: HAT, histone acetyltransferase; DBD, DNA-binding domain; HDAC, histone deacetylase; PIP, pyrrole-imidazole polyamides; DMSO, dried dimethylsulfoxide; IPA, ingenuity pathway analysis; GSEA, gene set enrichment analysis; KEGG, Kyoto encyclopedia of genes and genomes; ESI-TOF MS, electrospray ionization time-of-flight mass spectrometry, DMF, dimethylformamide; HPLC, high performance liquid chromatography; FBS, fetal bovine serum;

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