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Design, synthesis and biological evaluation dual inhibitors targeting G9a and HDAC as novel anticancer agents

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DNA is packaged with chromatin within the cell, the nucleosome is the fundamental unit of chromatin and it is composed of an octamer of the four core histones (H3, H4, H2A, H2B) around which 147 base pairs of DNA are wrapped. Posttranslational modifications(PTM) of histone tails such as acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation play important roles in epigenetic regulation[1]. These modifications are maintained by the relative activities of sequence-specific writers and erasers, with aberrant enzymatic activities or expression profiles closely correlated with multiple human Diseases. In this work we focused on developing a dual inhibitor targeting two PTMs: histone H3 lysine 9 (H3K9) methylation promoted by G9a and the overall histone deacetylation promoted by HDAC(Fig.1). These modifications are directly correlated with many cancers including leukemia, prostate carcinoma, hepatocellular carcinoma and lung cancer[2, 3]. In this work we bring forward a single molecule possesses the pharmacophore of a G9a inhibitor and HDAC inhibitor by substituting the lipophilic cap of the HDAC inhibitor with a G9a inhibitor core(Fig.2). Complex diseases like cancer have a multifactorial basis that involves both genetic and environmental risk factors, a balanced modulation of several therapeutic targets can provide a superior therapeutic effect and a lowered side effect profile compared with monotherapies.

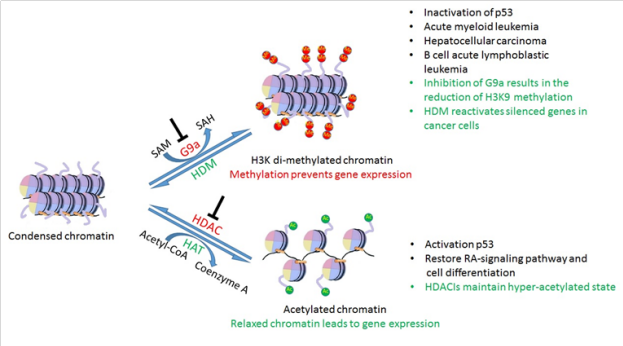

Fig.1An overview of post translational modifications on H3K9 and its significances in various cancer development.

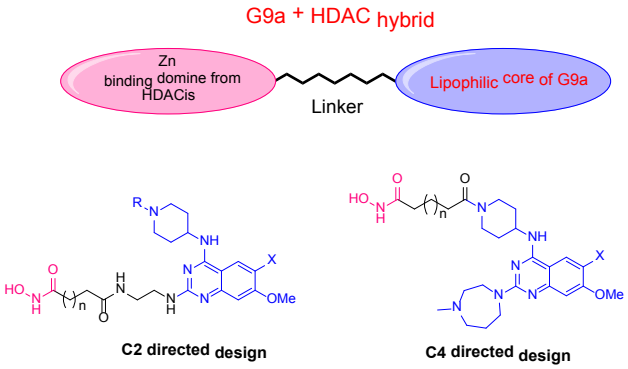

Fig.2 combinatorial compounds

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