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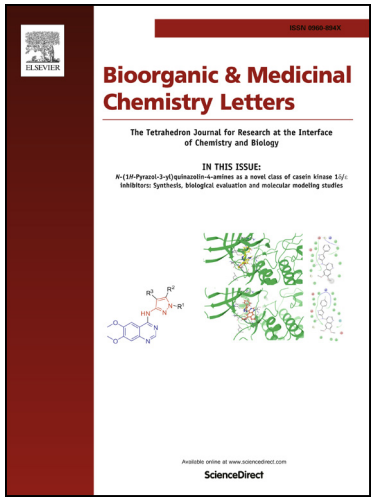

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PII: S0960-894X(17)30801-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.08.011
Reference: BMCL 25205

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 2 July 2017
Revised Date: 6 August 2017
Accepted Date: 7 August 2017

Please cite this article as: Xie, R., Li, Y., Tang, P., Yuan, Q., Rational design, synthesis and preliminary antitumor activity evaluation of a chlorambucil derivative with potent DNA/HDAC dual-targeting inhibitory activity, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.08.011

Rational design, synthesis and preliminary antitumor activity evaluation of a chlorambucil derivative with potent DNA/HDAC dual-targeting inhibitory activity

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ABSTRACT:

Histone deacetylases (HDACs) play a pivotal role not only in gene expression but also in DNA repair. Herein, we report the successful design, synthesis and evaluation of a chlorambucil derivative named vorambucil with a hydroxamic acid tail as a DNA/HDAC dual-targeting inhibitor. Vorambucil obtained both potent DNA and HDACs inhibitory activities. Molecular docking results supported the initial pharmacophoric hypothesis and rationalized the potent inhibitory activity of vorambucil against HDAC1, HDAC2 and HDAC6. Vorambucil showed potent antiproliferative activity against all the test four cancer cell lines with IC_{50} values of as low as 3.2~6.2 μM and exhibited 5.0~18.3 fold enhanced antiproliferative activity than chlorambucil. Vorambucil also significantly inhibits colony formation of A375 cancer cells. Further investigation showed that vorambucil remarkably induced apoptosis and arrested the cell cycle of A375 cells at G2/M phase. Vorambucil could be a promising candidate and a useful tool to elucidate the role of those DNA/HDAC dual-targeting inhibitors for cancer therapy.

Keywords: Chlorambucil; Nitrogen mustard; Hydroxamic acid; Anticancer

Genotoxic anticancer drugs play a key role in cancer treatment for many years. Among them, the nitrogen mustards represent a major class of genotoxic anticancer drugs for the treatment of various cancers. Chlorambucil as one of the best tolerated nitrogen mustards is in worldwide clinical use (Fig. 1A). The mechanism of action of chlorambucil is based on attacking cellular DNA and causing DNA damage.[1-3] However, the DNA damage caused by genotoxic drugs can be alleviated by cellular DNA repair machinery, so that some cancer cells can survive and eventually lead to treatment failure.[4-6] As a result, nitrogen mustards exhibited poor potency and limited treatment success. Inhibition of DNA repair machinery may be an effective strategy to enhance the efficacy of nitrogen mustards.

Histone deacetylases (HDACs) are a family of epigenetic enzymes with critical roles in chromatin condensation and gene expression by catalyzing the removal of acetyl groups from histones.[7-11] It has been shown that acetylation of the core histones weakens the histone-DNA interactions, thereby increasing DNA accessibility.[12] Recent evidence demonstrates that the structural alterations in chromatin induced by HDAC inhibitors could expose DNA to DNA-damaging agents such as ultraviolet rays, x-ray and genotoxic drugs, eventually leading to double strand breaks in DNA.[13-15] Inhibition of HDAC could down-regulate the DNA repair machinery.[16] The critical role