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PII: S0960-894X(17)30036-7
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.01.025
Reference: BMCL 24601

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 2 December 2016
Accepted Date: 9 January 2017

Please cite this article as: Idippily, N.D., Gan, C., Orefice, P., Peterson, J., Su, B., Synthesis of Vorinostat and cholesterol conjugate to enhance the cancer cell uptake selectivity, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.01.025

Revision BMCL-D-16-00829

Synthesis of Vorinostat and cholesterol conjugate to enhance the cancer cell uptake selectivity

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Abstract

Histone deacetylase (HDAC) inhibitors modulate various cellular functions including proliferation, differentiation, and apoptosis. Vorinostat (SuberAniloHydroxamic Acid, SAHA) is the first HDAC inhibitor approved by FDA for cancer treatment. However, SAHA distributes in cancer tissue and normal tissue in similar levels. It will be ideal to selectively deliver SAHA into cancer cells. Rapidly growing cancer cells have a great need of cholesterol. Low-density lipoprotein (LDL) is the major cholesterol carrier in plasma and its uptake is mediated by LDL-receptor (LDL-R), a glycoprotein overexpressed on the surface of cancer cells. Herein, we designed and synthesized a SAHA cholesterol conjugate, and further formed the conjugate containing particles with LDL as the carrier. The diameters of the particles were determined. The inhibitory activity of the particles carrying the conjugate was determined with cancer cell proliferation assay, and the hydrolysis of the conjugate by the enzymes in cancer cells was confirmed with LC-MS/MS.