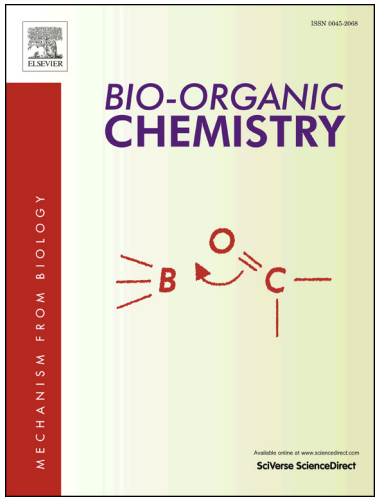

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PII: S0045-2068(16)30027-X
DOI: http://dx.doi.org/10.1016/j.bioorg.2016.03.008
Reference: YBIOO 1895

To appear in: *Bioorganic Chemistry*

Received Date: 3 March 2016
Revised Date: 16 March 2016
Accepted Date: 16 March 2016

Please cite this article as: V.T. Ha, V.T. Kien, L.H. Binh, V.D. Tien, N.T.T. My, N.H. Nam, M. Baltas, H. Hahn, B.W. Han, D.T. Thao, T.K. Vu, Design, synthesis and biological evaluation of novel hydroxamic acids bearing artemisinin skeleton, *Bioorganic Chemistry* (2016), doi: http://dx.doi.org/10.1016/j.bioorg.2016.03.008

Bioorganic Chemistry
journal homepage: www.elsevier.com/locate/bioorg

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Artemisinin
Histone deacetylase (HDAC) inhibitors
Hydroxamic acids
Endoperoxide
Cytotoxicity

ABSTRACT

A series of novel hydroxamic acids bearing artemisinin skeleton was designed and synthesized. Some compounds in this series exhibited moderate inhibition against the whole cell HDAC enzymes. Especially, compound **6g** displayed potent cytotoxicity against three human cancer cell lines, including HepG2 (liver cancer), MCF-7(breast cancer) and HL-60 (leukemia cancer), with IC_{50} values of 2.50, 2.62 and 1.28 µg/mL, respectively. Docking studies performed with two potent compounds **6a** and **6g** using Autodock Vina showed that both compounds bound to HDAC2 with relatively high binding affinities (from -7.1 to -7.0 kcal/mol) compared to SAHA (-7.4 kcal/mol). It was found in this research that most of the target compounds seemed to be more cytotoxic toward blood cancer cells (HL-60) than liver (HepG2), and breast (MCF-7) cancer cells.

1.Introduction

Target-based drug design and discovery currently attract a great deal of interest from medicinal chemists in anticancer drug discovery and development worldwide [1]. Many molecular targets for anticancer drugs have been identified, including deacetylases (HDACs) which are now considered to be an attractive target for anticancer drug design [2,3]. HDACs are enzymes that catalyse the removal of acetyl groups from specific lysine residues in the histone tails, and this leads to chromatin condensation and transcriptional repression [2,3]. HDACs have also been recognized to be involved in the regulation of gene expression and chromatin structure, and to have an important role in cell-cycle progression and the carcinogenic process [2,3]. So far, total 18 mammalian HDAC enzymes have been identified, and classified into four classes based on their structural and functional characteristics [4]. Deep and wide researches both in *in vitro* and *in vivo* preclinical models concerning inhibition effect of HDACs have shown that this effect results in cell differentiation, apoptosis, and cell-cycle arrest in a number of cancer cell lines [5-13]. HDAC inhibitors have, therefore, become a promising class of therapeutic agents that induce tumor cell cytostasis, differentiation and apoptosis in various hematologic and solid malignancies [8-11,14,15]. In fact, a lot of effort over the past decades has been done and brought about identification of many potent HDAC inhibitors, including SAHA (suberoylanilide hydroxamic acid, Vorinostat), PXD-01 (Belinostat), LBH-589 (Panobinostat), MS-27-527 (Entinostat), and romidepsin (Fig. 1) [13,16,17]. More recently, two HDAC inhibitors including SAHA (trade name, Zolinza®) and romidepsin (tradename, Istodax®) (Fig. 1) have been approved by the FDA in 2006 and 2009, respectively, to treat cutaneous T-cell lymphoma. We have also investigated a series of 2-oxoindoline-based hydroxamic acids (Fig. 2) and screened for their HDAC inhibitory effects as well as cytotoxic activity. Some compounds displayed potent cytotoxicity against three human cancer cell lines, including SW620 (colon cancer), PC-3 (prostate cancer) and AsPC-1 (pancreatic cancer), with IC_{50} values as low as 0.05-0.07µM, 74-fold lower than that of SAHA (1.64-3.70 µM) (Fig 2) [18].

Artemisinin (**1**) (Fig. 1), a sesquiterpene lactone endoperoxide, isolated from *Artemisia annua* L and its oil and water-soluble derivatives such as artemether, arteether, and artesunate are effective antimalarial agents, especially against multi-drug resistant malarial strains [19]. Recently, besides the antimalarial activity, artemisinin derivatives have received much attention in the search for new anticancer agents due to the similar mechanisms underlying both antitumor and antimalarial properties [20,21]. Some artemisinin analogues showed very potent cytotoxicity against several cancer cell lines [22-25]. Regarding the drug design, the strategy of the multi-target

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