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Original article

Novel hybrids from *N*-hydroxyarylamide and indole ring through click chemistry as histone deacetylase inhibitors with potent antitumor activities

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ABSTRACT

Novel hybrid molecules **8a–8o** were designed and synthesized by connecting indole ring with *N*-hydroxyarylamide through alkyl substituted triazole, and their *in vitro* biological activities were evaluated. It was discovered that most of target compounds showed promising anticancer activities, particularly for **8n**, which had a significant HDACs inhibitory and antiproliferative activities comparable to or slightly stronger than SAHA against human carcinoma cells. Furthermore, compound **8n** exhibited much better selectivity for HDAC1 over HDAC6 and HDAC8 than SAHA. In addition, compound **8n** also could dose-dependently induce cancer cell cycling arrest at G0/G1 phase and promote the expression of the acetylation for histone H3 and tubulin *in vitro*. Therefore, our novel findings may provide a new framework for the design of new selective HDAC inhibitor for the treatment of cancer.
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1. Introduction

Epigenetics is widely implicated in tumor initiation and progression by different modifications of DNA and histones [1,2]. There is a growing body of evidence demonstrating the importance of histone modification in silencing tumor suppressor genes [3]. Histone acetylation and deacetylation play crucial roles for regulating protein function of eukaryotic cells, which are correlated with two classes of enzymes: Histone acetyltransferases (HATs) and histone deacetylases (HDACs) [4]. HATs add acetyl groups to lysine residues of histone tails causing localized relaxation of chromatin and transcriptional activation of nearby genes, while HDACs remove the acetyl groups of acetylated histones leading to transcriptional repression [4,5]. The maintenance of equilibrium between acetylation and deacetylation of histones and non-histone substrates is essential for normal cell growth. However, HDAC overexpression has been found in a variety of human cancers and inflammation, including myeloid neoplasia and solid tumors [6]. HDACs play important roles in the upstream control of gene transcription, cell cycle progression, and apoptosis. Consequently, it has been widely recognized that HDACs are promising targets for intervention of a number of cancers [7–9].

It is known that histone deacetylase inhibitors (HDACi) have been shown to induce cell growth arrest, differentiation and/or apoptosis in different cancer cell lines. More encouragingly, the suberoylanilide hydroxamic acid (SAHA, Vorinostat, Fig. 1) has been licensed for the treatment of cutaneous T cell lymphoma treatment (CTCL) on 2006 [10]. In November 2009, FDA also approved romidepsin (FK228) for treatment of CTCL in patients who have received at least one prior systemic therapy [11]. These two approved drugs have validated the therapeutic use of HDAC inhibitors in cancer therapy.

There are a number of new HDACi that are currently undergoing various stages of clinical development for therapy of multiple cancer types [9,12,13]. The common pharmacophore of these HDACi consists of three domains: A zinc-binding group (ZBG), such as hydroxamic acid; a cap group, generally a hydrophobic and aromatic group; a saturated or unsaturated linker domain, composed of linear or cyclic structures that connect the ZBG and the cap group [14]. HDAC inhibitors are grouped chemically into four classes: Hydroxamic acids, benzamides, short-chain fatty acids, and cyclic tetrapeptides [15]. To date, many studies on HDACi development have focused on the arylhydroxamic acids. Among these *N*-hydroxyarylamide derivatives, Belinostat

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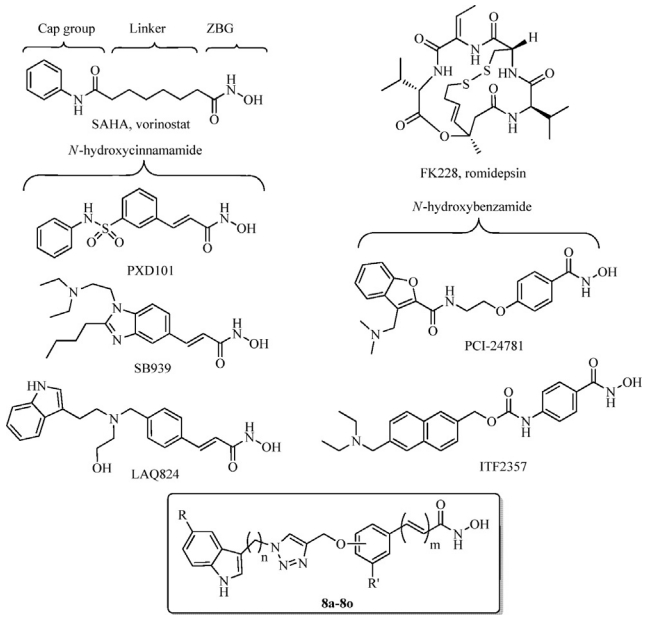

Fig. 1. Structures of representative HDAC inhibitors and target compounds **8a–8o**.

(PXD101), pracinostat (SB939), and dacinostat (LAQ824) in clinical trials share a common active fragment *N*-hydroxycinnamamide (see Fig. 1), and exhibited excellent HDAC inhibitory activity [16–18]. In addition, abexinostat (PCI-24781) and givinostat (ITF2357) with an *N*-hydroxybenzamide moiety are currently undergoing clinical trials [19,20].

Although HDACis showed potent antitumor effects, they also exhibited side effects that might limit their clinical potential [21]. Therefore, looking for new HDACis that are specific-inhibition to one kind HDAC subtype is extremely urgent and necessary. As part of our ongoing effort to discover novel anticancer agents, we were inspired by the fact that many natural or synthetic products bearing indole rings usually display excellent antiproliferative activities against several cancer cells in recent years [22,23]. More importantly, some HDACis containing the indole ring as cap group also show prominently the clinical therapeutic effect of cancer [18,24]. In addition, it is well-known that click chemistry has been widely applied in organic synthesis and drug discovery to afford a highly efficient combinatorial approach to construct a library of new HDACi candidates [25,26]. And the triazole ring is often used as a cap group, which may have favorable π–π stacking interactions with phenylalanine residues of HDACs. With these ideas in mind, the novel target compounds **8a–8o** were designed and synthesized by connecting indole ring with *N*-hydroxyarylamide through alkyl substituted triazole. We proposed that the triazole ring could act as a linking moiety which joins the cap group to the linker group in the structure of HDACi. Here we report the synthesis and biological evaluation of the target compounds.

2. Experimental

Melting points were determined on a RDCSY-I capillary apparatus and were uncorrected. The compounds synthesized were purified by column chromatography using silica gel (200–300 mesh) except for recrystallization and thin-layer chromatography (TLC) using silica gel 60 F_{254} plates (250 mm; Qingdao Ocean Chemical Company, China). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance spectrometer at 300 K, using TMS as an internal standard. MS spectra were recorded on a Mariner Mass Spectrum (ESI) and HRMS on Agilent technologies LC/MSD TOF.

The synthetic route of these target compounds **8a–8o** is outlined in Scheme 1. The key reaction in the synthesis of the target compounds is the click chemistry between azides and terminal alkynes [27]. On the one hand, the indole bromide **1a–1c** were reacted with NaN_3 to generate indole azides **2a–2c** in MeCN solution. On the other hand, various hydroxyl substituted methyl cinnamate **3a–3e** were treated with 3-bromoprop-1-yne to obtain etherified alkynes **4a–4e**, which subsequently were reacted with indole azides **2a–2c** to give key intermediates **5a–5o** in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate by click chemistry. Next, intermediates **5a–5o** were subsequently hydrolyzed to obtain **6a–6o**, which were directly treated with tetrahydro-2*H*-pyran-2-ol to form compounds **7a–7o** in the presence of *N*-methylmorpholine and ethyl chloroformate. Finally, *O*-protected groups of **7a–7o** were removed by CF_3COOH (TFA) to provide target compounds **8a–8o**. The products **8a–8o** were purified by column chromatography, and their structure data of MS, ^{1}H NMR spectra and HRMS of selected compounds were shown in reference [28].

General synthetic procedure for **2a–2c**: A mixture of indole bromide **1** (10 mmol) and NaN_3 (0.78 g, 12 mmol) in 50 mL acetonitrile was refluxed for 3 h. The solvent was evaporated in vacuum and water was added. The solution was then extracted with ethyl acetate (50 mL, 3×). The organic layer was concentrated *in vacuo* to yield **2a–2c** as yellowish oil (81%–85%).

General synthetic procedure for **4a–4e**: A mixture of **3a–3c** (5 mmol), K_2CO_3 (0.7 g, 5 mmol) and KI (83 mg, 0.5 mmol) in acetonitrile (40 mL) was refluxed and stirred for 3–6 h. The solvent was evaporated in vacuum and water was added. The solution was then extracted with ethyl acetate (40 mL, 3×). The organic layer was combined, washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*, affording **4a–4e** as pale yellow solid (72%–78%).

General synthetic procedure for **5a–5o**: A mixture of **3a–3c** (3 mmol), $CuSO_4{\cdot}5H_2O$ (0.30 g, 1.2 mmol) and sodium ascorbate (0.36 g, 1.8 mmol) in DMF (40 mL) was stirred for 3–5 h at 80 °C. The solution was then cooled, and poured into 200 mL water, which was subsequently extracted with ethyl acetate (50 mL, 3×). The organic layer was combined, washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate = 5:1–2:1, v/v as the eluent) to give **5a–5o** as white solid (66%–75%).

General synthetic procedure for **7a–7o**: To a solution of **5a–5o** (1.2 mmol) in methanol (20 mL), 1 mol/L NaOH (3.2 mL) was dropwised added. The mixture was refluxed for 2–4 h, and then cooled. The solvent was evaporated and the residue was dissolved in water. The mixture was acidified with 2 mol/L HCl solution to pH 5. The precipitate was filtered, washed with water, and dried in vacuum to afford the crude, which was subsequently added into a solution of *N*-methylmorpholine (0.12 g, 1.4 mmol) and ethyl carbonochloridate (0.13 g, 1.2 mmol) in 20 mL anhydrous THF at 0 °C. Next, the mixture was stirred at room temperature for 1 h, which was then added dropwise to a solution of tetrahydro-2*H*-pyran-2-ol (0.14 g, 8 mmol) in 5 mL anhydrous THF. After the reaction was completed, the resulting mixture was allowed to pour into ice-water, and extracted with ethyl acetate (20 mL, 3×). The organic phase was washed with water and brine, then dried over anhydrous sodiumsulfate, filtered and evaporated to afford the crude product, which was purified by column chromatography on silica gel to give compound **7a–7o** as pale yellow waxy solid (53%–66%).

General synthetic procedure for **8a–8o**: A solution of **7a–7o** (0.70 mmol) and CF_3COOH (1 mL) in 5 mL dry CH_2Cl_2 was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The crude residue was dissolved in 10 mL dichloromethane and 2 mL Et_3N was slowly added to the solvent, and the

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