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Development of novel ferulic acid derivatives as potent histone deacetylase inhibitors

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ABSTRACT

Histone deacetylase inhibitors (HDACIs) offer a promising strategy for cancer therapy. The discovery of potent ferulic acid-based HDACIs with hydroxamic acid or 2-aminobenzamide group as zinc binding group was reported. The halogeno-acetanilide was introduced as novel surface recognition moiety (SRM). The majority of title compounds displayed potent HDAC inhibitory activity. In particular, **FA6** and **FA16** exhibited significant enzymatic inhibitory activities, with IC_{50} values of 3.94 and 2.82 μM, respectively. Furthermore, these compounds showed moderate antiproliferative activity against a panel of human cancer cells. **FA17** displayed promising profile as an antitumor candidate. The results indicated that these ferulic acid derivatives could serve as promising lead compounds for further optimization.

1. Introduction

Histone deacetylases (HDACs) are zinc metalloenzyme which remove acetyl group of lysine residues located on nucleosomal histones. Histone acetylation and deacetylation are essential in modulation of chromatin topology and gene transcription. HDACs are critical in the epigenetic regulation of gene expression.[1] They could cause condensation of chromatin resulting in transcriptional repression. Therefore, HDACs play an essential role in cell proliferation, cell-cycle regulation and apoptosis.[2] Aberrant activity of HDACs has been found in several human cancers leading to development of histone deacetylase inhibitors (HDACIs). As clinically validated cancer targets, their inhibition has been proven to be successful strategy for the development of novel anticancer agents.[3]

Moreover, HDACIs exhibit attractive antitumor properties by inducing transcriptional events involved in growth arrest, cell proliferation, and apoptosis.[4] There are numbers of HDACIs emerging as an exciting novel class of antitumor agents (Fig. 1). Suberoylanilide hydroxamic acid (Vorinostat, SAHA) is the first HDACI approved by FDA in 2006. Belinostat and Panobinostat are also hydroxamate HDACIs which induce acetylation of histone at nanomolar concentrations. Entinostat is an oral benzamide HDACI with limited cardiac toxicity in preclinical studies.[5]

HDACIs are classified into different classes depending on their structures namely aliphatic acids, hydroxamic acids, 2-aminoanilides, cyclic peptides and electrophilic ketones.[6] These structures all shared common pharmacophore composed of four portions: (a) zinc binding group (ZBG), which chelates zinc ion at the bottom of pocket, (b) linker (scaffold), usually hydrophobic which occupies the narrow channel, (c) connect unit (CU), which connects SRM and linker, (d) surface recognition moiety (SRM), which interacts with residues on the rim of active site (Fig. 1). The common linkers are aliphatic chain, aromatic chain and vinyl-aromatic chain. The most common ZBGs are hydroxamic acid and 2-aminobenzamide.[7] In the past two decades, a number of HDACIs have been developed by modifying of SRM, linker and ZBG. However, recent studies have focused on varying SRM or linker portion. Based on the common pharmacophore, we designed and synthesized a series of ferulic acid-based HDACIs.

Ferulic acid (Fig. 2) is a natural product isolated from many staple foods, including fruits, vegetables, cereals, and coffee.[8] Ferulic acid and its derivatives displayed broad range of therapeutic effects, with applications including anticancer, antidiabetic, cardio protective, neuroprotective, and antiinflammatory activity. Herein, we introduced rigid ferulic acid as linker of HDACIs.

In our earlier work, structural optimization of natural alkaloid taspine afforded a novel antitumor agent (**HMQ1611**, Fig. 2).[9] It displayed antiproliferative activity against several human cancer cell lines. Moreover, numbers of acetanilides with halogen substituents were prepared and exhibited potent anticancer activity.[10] We supposed that halogeno-acetanilide might be suitable as SRM of HDACIs. We focused our attention on searching for novel ferulic acid derivatives with halogeno-acetanilide as SRM. It provides opportunities to develop potent HDACIs. These novel HDACIs comprising common hydroxamic acid or 2-aminobenzamide group as ZBG (Fig. 2).

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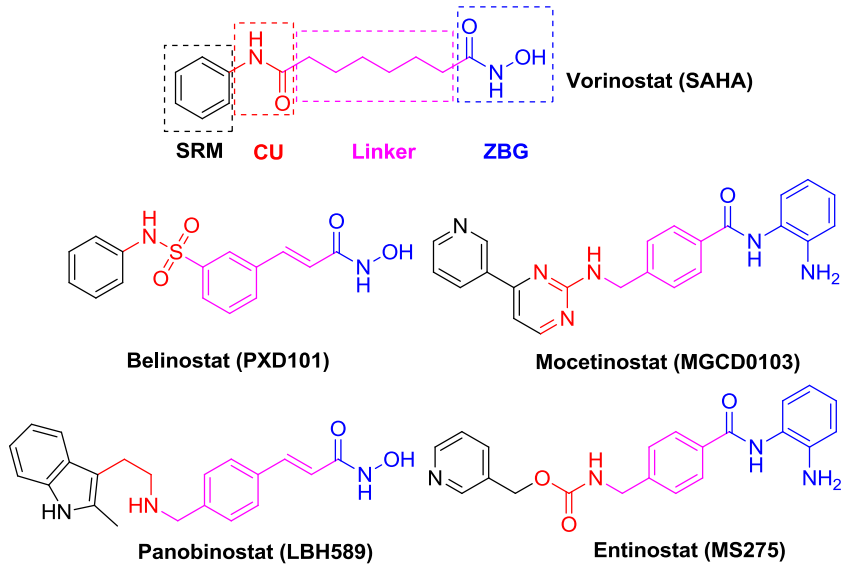


Figure 1. Structures and pharmacophore features of HDACIs.

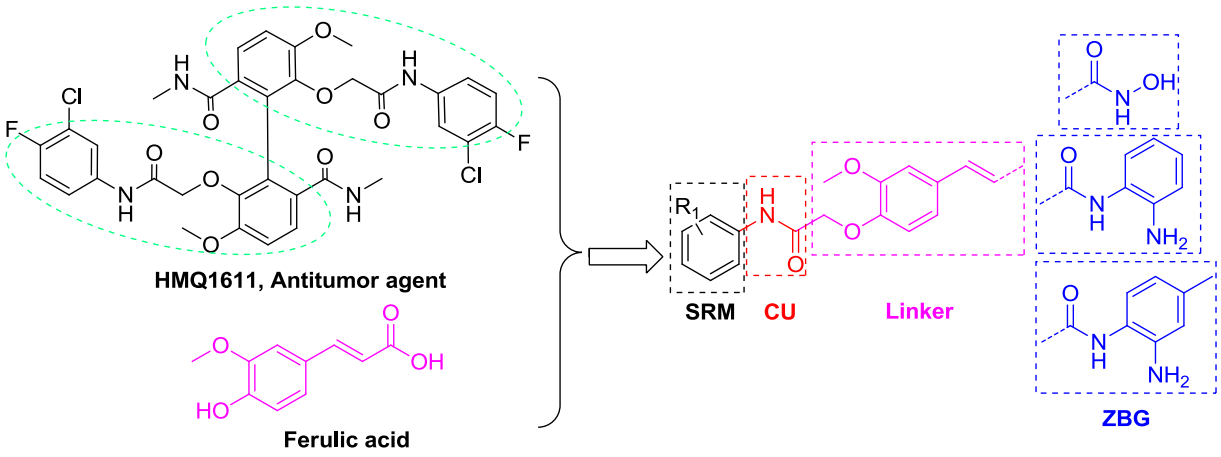


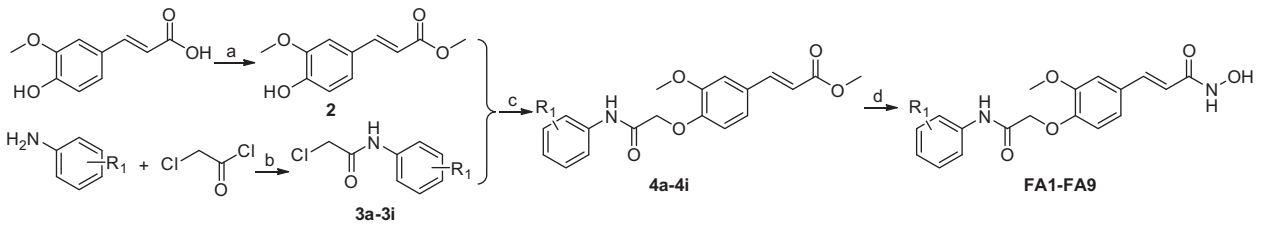
Figure 2. Design strategy and structures of target compounds.

As part of our ongoing effort to develop antitumor agents, we developed two series of ferulic acid derivatives bearing halogenoacetanilide as SRM. Various anilines were used to investigate the role of R_1 substituent. The structures of these compounds are quite consistent with common pharmacophore of HDACIs (Fig. 2). The binding mode of the two most potent compounds with HDAC was also established.

2. Chemistry

All the title compounds were prepared from commercial available ferulic acid. An efficient synthesis of hydroxamic acids was developed in 4-step reaction sequence (Scheme 1). Ferulic acid was esterified in the presence of concentrated H_2SO_4 to afford ferulic acid methylester **2**. Various substituted anilines were acylated with chloroacetyl chloride in polar solvent to provide intermediates **3a–3i**. The hydroxyl group in **2** was etherified with haloacylanilines **3a–3i** in anhydrous acetone in the presence of K_2CO_3 to afford corresponding intermediates **4a–4i**.[11] The resulting esters **4a–4i** were treated with methanolic NH_2OK at room temperature to yield corresponding hydroxamic acid derivatives **FA1–FA9**.[12]

Scheme 2 exhibited synthetic route of ferulic acid derivatives bearing 2-aminobenzamide. Ferulic acid was converted into its imidazolide derivative by reaction with *N,N′*-carbonyldiimidazole



Scheme 1. Preparation of compounds **FA1–FA9**. Reagents and conditions: (a) CH_3OH, H_2SO_4; (b) CH_2Cl_2, Et_3N; (c) K_2CO_3, acetone; (d) NH_2OK, NH_2OH, DMF.