European Journal of Medicinal Chemistry 122 (2016) 92–101

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

2-(Phenylsulfonyl)quinoline *N*-hydroxyacrylamides as potent anticancer agents inhibiting histone deacetylase

Hsueh-Yun Lee [a], Chih-Yi Chang [a], Chih-Jou Su [b], Han-Li Huang [b], Samir Mehndiratta [a], Yuh-Hsuan Chao [a], Chia-Ming Hsu [b], Sunil Kumar [a], Ting-Yi Sung [b], Yi-Zhen Huang [b], Yu-Hsuan Li [a], Chia-Ron Yang [c, **], Jing-Ping Liou [a, *]

[a] School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 11031, Taiwan
[b] The Ph.D. Program for Cancer Biology and Drug Discovery, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan
[c] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 22 February 2016
Received in revised form
26 May 2016
Accepted 14 June 2016
Available online 16 June 2016

Keywords:
Anticancer agents
Histone deacetylase inhibitors
2-(Phenylsulfonyl)quinoline

ABSTRACT

This study reports the design and synthesis of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides (**8a**–**k**). Structure-activity relationship studies focusing on regio-effect of *N*-hydroxyacrylamide moiety and influence of the sulfonyl linker revealed that *N*-hydroxy-3-[3-(quinoline-2-sulfonyl)-phenyl]-acrylamide (**8f**) showed remarkable enzymatic and cellular activity. The GI_{50} values of **8f** for HL-60, HCT116, PC-3, and A549 cells were found to be 0.29, 0.08, 0.15, and 0.27 μM, respectively. The compounds are therefore more potent than FDA approved PXD-101 and SAHA. They also have an effect on the acetylation degree of histone H3 and α-tubulin. In *in vivo* studies, **8f** showed marked inhibition of the growth of HCT116 xenografts.

1. Introduction

Histone deacetylases (HDACs) which are involved with the degree of acetylation of histone, have been identified as a crucial target for cancer therapy. Acetylation of histone, a covalent modification, also named an epigenetic process, is regulated by two classes of enzymes, histone acetyltransferase (HAT) and histone deacetylase (HDAC) [1,2]. The balance between these controls is highly correlated with development of cancer. The use of HDAC inhibitors helps restore the aberrant epigenetic process and consequently, HDAC has become a significant target for cancer therapy. To date, the U.S Food and Drug Administration has approved several HDAC inhibitors for various indications. These include SAHA (vorinostat) and FK-228 (romidepsin) for the treatment of refractory cutaneous T-cell lymphoma [3,4], PXD101 (belinostat) for treatment of refractory peripheral T-cell lymphoma [5], and LBH589 (panobinostat) for the treatment of multiple myeloma [6] (see Fig. 1).

All of these compounds possess a distinct moiety such as hydroxamic acid or 2-aminophenylamide, and such moieties are felt to be characteristic of HDAC inhibitors [7]. Hydroxamic acid has been widely used in the development of HDAC inhibitors and the structures of PXD-101 and LBH589, both possess a *N*-hydroxyacrylamide moiety (C═C–CO–NH–OH, bold in Fig. 2). Our previous work on 1-arylsulfonyl-5-(*N*-hydroxyacrylamide)indoles (**5a**) [8], 1-arylsulfonyl-5-(*N*-hydroxyacrylamide)indolines (**5b**) [9,10], azaindolylsulfonamides (**6**) [11], and 1-arylsulfonyl-5-(*N*-hydroxyacrylamide)tetrahydroquinolines (**7**) [12], suggests that the *N*-hydroxyacrylamide moiety is associated with significant HDAC inhibitory activity. Compounds (**5**–**7**) that we reported previously have three components (Fig. 2): a heterocycle (blue), a benzenesulfonyl group (purplish red), and an *N*-hydroxyacrylamide moiety (bold). In these cases, the heterocycles are linked to a benzenesulfonyl group forming a sulfonamide group. In the current study our plan was to assemble these two components providing an alternative link between the heterocycle and the benzenesulfonyl group, forming non-sulfonamide molecules. In this way, we synthesized a series of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides (**8a**–**k**) and studied their structure-activity relationships. The influence of the sulfonyl linker and the regio-effect of *N*-hydroxyacrylamide on antiproliferative activity were also investigated.

* Corresponding author.
** Corresponding author.
E-mail addresses: cryang@ntu.edu.tw (C.-R. Yang), jpl@tmu.edu.tw (J.-P. Liou).

http://dx.doi.org/10.1016/j.ejmech.2016.06.023
0223-5234/

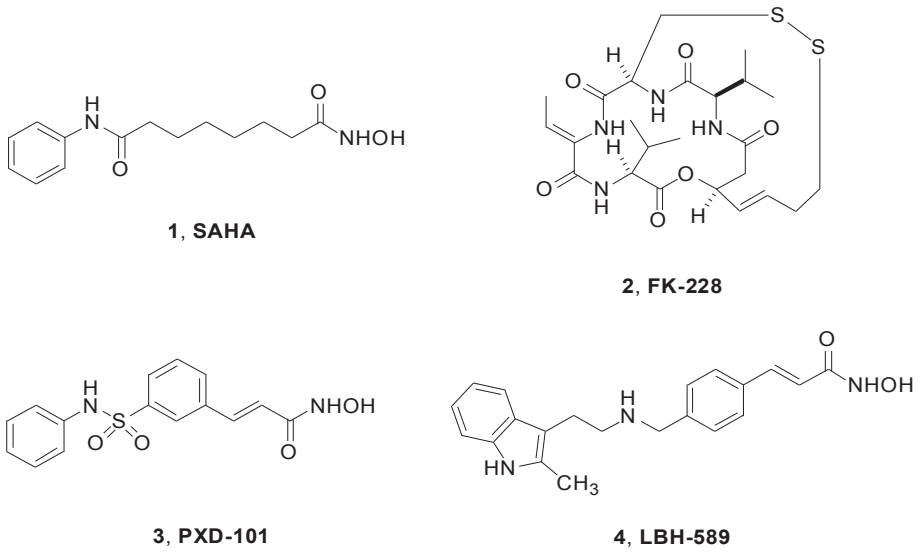

Fig. 1. FDA-approved HDAC inhibitors.

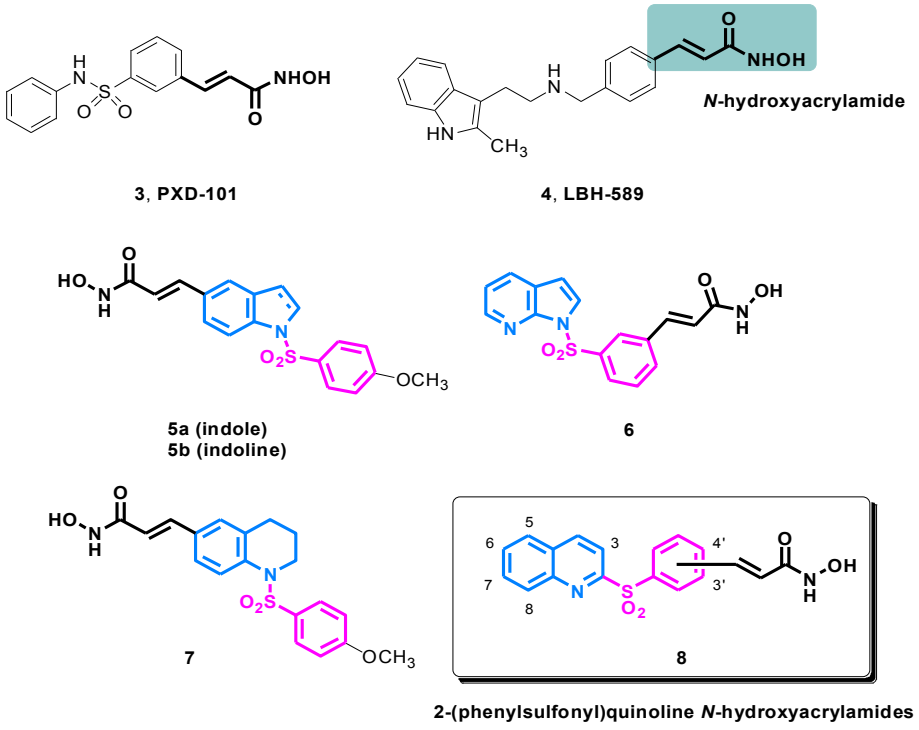

Fig. 2. Design of 2-(phenylsulfonyl)quinoline *N*-hydroxyacrylamides.

2. Results and discussion

2.1. Chemistry

The general route used for the synthesis of 2-(phenylsulfonyl) quinoline *N*-hydroxyacrylamides (**8a**–**k**) is described in Scheme 1. Different 2-chloroquinolines (**9a**–**j**) were reacted with substituted thiophenols under basic conditions and this was followed by oxidation with *m*-CPBA, yielding the 2-(phenylsulfonyl)quinolines (**10a**–**k**). The resulting products underwent Heck olefination with *tert*-butyl acrylate to afford compounds **11a**–**k**, which were subjected to hydrolysis by TFA to yield the corresponding carboxylic acids (**12a**–**k**). Compounds **12a**–**k** were then reacted with NH_2OTHP in the presence of EDC·HCl followed by hydrolysis with 10% TFA to produce the target compounds (**8a**–**k**). Compounds **18a**–**b**, in which the sulfonyl has been replaced by a carbonyl group, were synthesized according to the method shown in Scheme 2. Quinoline-2-carbaldehyde (**13**) underwent nucleophilic addition with (3-(diethoxymethyl)phenyl)magnesium bromide or (4-(dimethoxymethyl)phenyl)- magnesium bromide followed by oxidation with pyridinium dichromate (PDC) to obtain the 2-benzoylquinolines (**14a**–**b**). Subsequently, the dialkoxymethyl groups in **14a** and **14b** were hydrolyzed under acidic condition to provide the corresponding benzaldehydes (**15a**–**b**). The