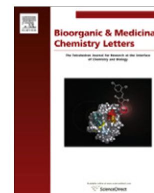
Bioorganic & Medicinal Chemistry Letters 21 (2011) 5735–5738

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl



2,5-Disubstituted-1,3,4-oxadiazoles/thiadiazole as surface recognition moiety: Design and synthesis of novel hydroxamic acid based histone deacetylase inhibitors

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ARTICLE INFO

Article history:
Received 25 May 2011
Revised 31 July 2011
Accepted 3 August 2011
Available online 8 August 2011

Keywords:
1,3,4-Oxadiazoles
1,3,4-Thiadiazoles
Anticancer activity
Histone deacetylase inhibitors

ABSTRACT

The enzymatic inhibition of histone deacetylase activity has come out as a novel and effectual means for the treatment of cancer. Two novel series of 2-[5-(4-substitutedphenyl)-[1,3,4]-oxadiazol/thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid (tetrahydro-pyran-2-yloxy)-amides were designed and synthesized as novel hydroxamic acid based histone deacetylase inhibitors. The antiproliferative activities of the compounds were investigated in vitro using histone deacetylase inhibitory assay and MTT assay. The synthesized compounds were also tested for antitumor activity against Ehrlich ascites carcinoma cells in Swiss albino mice. The efforts were also made to establish structure–activity relationships among synthesized compounds. The results of the present studying indicates 2,5-disubstituted 1,3,4-oxadiazole/thiadiazole as promising surface recognition moiety for development of newer hydroxamic acid based histone deacetylase inhibitor.

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Epigenetics indicates to a phenomenon in which gene expression can be changed by reversible chemical modifications to DNA or nucleosomal core histones. The acetylation of lysine side chains of histone tails is one of the most studied epigenetic activity. It is carried out by a family of histone acetyltransferases (HATs) and reversed by histone deacetylases (HDACs).[1–4]

The alterations in the structure or expression of HDACs have been clearly linked to the pathogenesis of cancer and successively HDAC inhibitors (HDACi) have emerged as a novel class of anticancer agents.[5–7] HDACi selectively induce growth arrest, differentiation, and apoptosis in tumor cells via transcriptional activation of a small set of genes that control cell proliferation and cell cycle development like p21.[8–10]

In 2006, Zolinza™ (SAHA, vorinostat) became the first HDACi to acquire FDA approval and is used for the management of the cutaneous manifestations of T-cell lymphoma. HDACi generally conform to a broadly accepted pharmacophore. The crystallographic studies for the design of valuable HDACi have pointed out three structural requirements[11]: a cap group (A) that provides interaction with the pocket entrance, a terminal group (B) that can bind to the zinc ion at the bottom of the active site, also known as zinc binding group (ZBG), and between both, a linker (C) fitting the tube-like portion of the binding pocket[12] (Fig. 1).

The common ZBG of HDACi is the hydroxamate moiety. Its structural modifications have been successful with isosteres such as benzamide, electrophilic ketones, mercaptoamide, α-ketoesters, and phosphonates.[13–15] Hence, the cap group offers an alternative prospect to discover potent and more selective HDACi. In the present study, 2,5-disubstituted-1,3,4-oxadiazole/thiadiazole has been employed as cap group in hydroxamate based HDACi possessing pyrimidine as a cyclic linker. This cap group was selected with two major concepts, that is, it could serve as an isostere to amide, ketone, and other groups possessing troublesome pharmacokinetic and toxic properties. Secondly, it could result in better cap group interactions with the amino acid side chains at the opening of the HDAC active site.

The 1,3,4-oxadiazole/thiadiazole nucleus represents an important core structure found in biologically active small molecules reported to possess anticancer activity.[16–18] Like many other heterocyclic aromatic structures, 2,5-disubstituted 1,3,4-oxadiazole/thiadiazole core provides numerous avenues for further chemical modifications. Thus, it was interesting to design hydroxamic acid based HDACi containing 1,3,4-oxadiazole/thiadiazole as surface recognition moiety.

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doi:10.1016/j.bmcl.2011.08.022

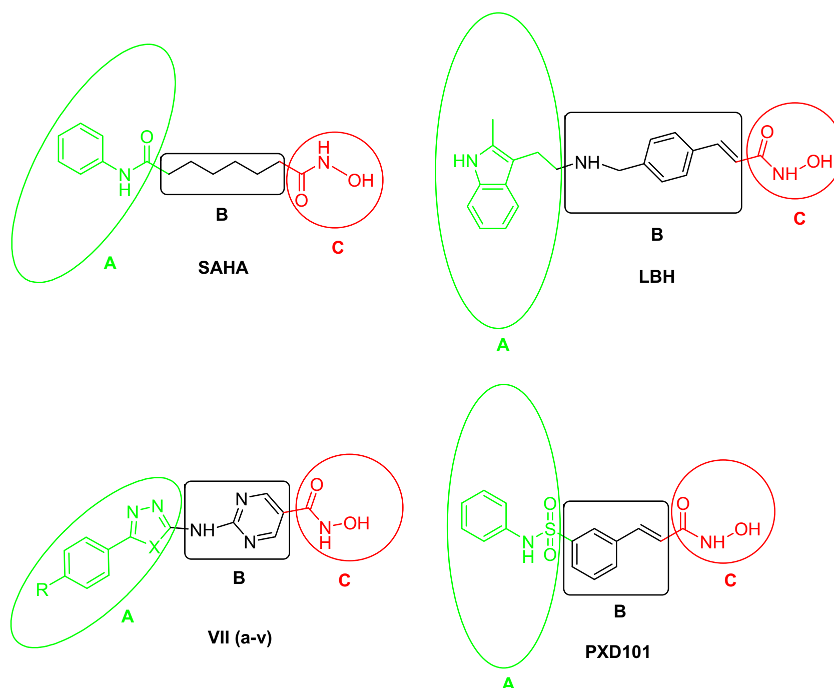

Figure 1. Presence of pharmacophoric elements in clinically established drugs and **VII** (**a**–**v**). A, surface recognition moiety (green color); B, linker (black color); and C, zinc binding group (red color).

The title compounds were prepared using the synthetic strategy described in Scheme 1. The required semicarbazones **II** (**a**–**k**) and thiosemicarbazones **II** (**l**–**v**) were synthesized from various aromatic aldehyde (**I**) according to reported procedure.[19,20] The compound **II** (**a**–**k**) were reacted with bromine (oxidative cyclization) in the presence of sodium acetate resulted in the formation of corresponding 2-amino-5-Aryl-1,3,4-oxadiazoles **III** (**a**–**k**).[21] The compound **II** (**l**–**v**) were cyclized to 2-amino-5-Aryl-1,3,4-thiadiazoles **III** (**l**–**v**) using ferric chloride.[20] Compound **III** (**a**–**v**) were reacted with 2-methylsulfonyl-5-pyrimidinecarboxylic acid ethyl ester to yield 2-[5-(4-substitutedphenyl)-[1,3,4]-oxadiazol/thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid ethyl ester **IV** (**a**–**v**). The 2-[5-(4-substitutedphenyl)-[1,3,4]-oxadiazol/thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid **V** (**a**–**v**) were synthesized from **IV** (**a**–**v**) on saponification with sodium hydroxide. The compound **V** (**a**–**v**) on reaction with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine yielded 2-[5-(4-substitutedphenyl)-[1,3,4]-oxadiazol/thiadiazol-2-ylamino]-pyrimidine-5-carboxylic acid (tetrahydro-pyran-2-yloxy)-amides **VI** (**a**–**v**). In the last step, title compounds **VII** (**a**–**v**) were prepared by removal of the tetrahydropyranyl (THP) protecting moiety in the presence of trifluoroacetic acid.[22]

All the synthesized compounds were tested for their ability to inhibit HDAC-1 activity and antiproliferative activity by MTT assays. The HDAC-1 was chosen since it is widely implicated in both transcriptional repression and chromatin remodeling. Test compounds exhibited significant activity in HDAC-1 inhibitory assay indicating that their anticancer property is due to inhibition of histone deacetylase-1. Inhibition of HDAC-1 causes apoptosis leading to anticancer activity.[23] The Mitomycin-C was chosen as standard drug in vivo anticancer studies as its mechanism of action involves apoptosis.[24] The assay of HDAC-inhibitory activity was assessed using the commercially available HDAC fluorescence activity assay/drug discovery (*Fluor de Lys*) kit (AK-500, BIOMOL Research Laboratories) according to the supplier's protocol. The IC_{50} of SAHA and TSA was reported to be 0.290 and 0.016 μM, respectively.[25] The antiproliferative activity of test compounds was evaluated by MTT assays.[26] HCT-116 cells were chosen for MTT assays because they have a high level of HDAC expression. The test compounds were evaluated in vivo for their anticancer activity against Ehrlich ascites carcinoma cells in Swiss albino mice as per reported procedure.[27,28] The tumor weight inhibition (TWI) and tumor cell inhibition (TCI) were measured as parameter for anticancer evaluation.

The results of in vitro anticancer studies shows that in oxadiazole series **VII** (**a**–**k**), compound **VII** (**e**) displayed maximum HDAC inhibitory activity with an IC_{50} = 0.017 μM against HDAC-1 and an IC_{50} = 0.28 μM in HCT-116 cell proliferation assay, while in thiadiazole series **VII** (**l**–**v**), compound **VII** (**p**) exhibited maximum HDAC inhibitory activity with an IC_{50} = 0.018 μM against HDAC-1 and an IC_{50} = 0.31 μM in HCT-116 cell proliferation assay (Table 1). In terms of potency of synthesized compounds, almost similar results were obtained during in vivo anticancer studies against Ehrlich ascites carcinoma cells in Swiss albino mice. The compound **VII** (**e**) (%TWI = 85.7; %TCI = 77.7) and **VII** (**p**) (%TWI = 75.0; %TCI = 76.8) were found most potent in oxadiazole and thiadiazole series of compounds, respectively (Table 2).

On correlating the structures of the synthesized compounds with their biological activity, it has been observed that compounds bearing the groups like hydroxyl, methoxy on phenyl ring attached to 1,3,4-oxadiazole/thiadiazole possess high potency in in vitro and in vivo anticancer evaluation. On the other hand, replacement of these groups with fluoro or chloro groups resulted in compounds with lesser antiproliferative activity. On comparison of results, it has been found that antitumor activity of test compounds changes on varying *para*-substituted group on aryl moiety attached to 1,3,4-oxadiazole/thiadiazole as follows: hydroxy > methoxy > methyl > amino > dimethylamino > nitro > chloro > fluoro > no substitution. It is to be noted that *para*-chloro analogs, that is, **VII** (**b**) and **VII** (**m**) showed greater potency than parent compound, that is, **VII** (**a**) and **VII** (**l**) in HDAC inhibition and MTT assay. The position of the substitution had dramatic effects on the HDAC activity. *Ortho*- and *meta*-chloro analogs, that is, **VII** (**h**), **VII** (**i**), **VII** (**s**), and **VII** (**t**) was found to be lesser active than *para*-chloro analogs. This might be attributed to unfavorable steric effect of *meta*- and *ortho*-substitution or to exceeding the optimum

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