Histone deacetylases (HDACs) are a class of zinc-dependent metalloproteinases that catalyze the removal of acetyl groups from lysine residues on histones and non-histone proteins. This action results in a “closed” chromatin configuration, thereby regulating the expression of genes, which include tumor suppressor genes (1,2). HDAC inhibitors (HDACIs) have attracted a great deal of interest as anticancer drug agents. Over the past 10 years, over 490 clinical trials of more than 20 HDACI candidates as anticancer agents have been conducted. Three HAACIs, vorinostat (SAHA, Zolinza®), romidepsin (FK-228, Istodax®), and belinostat (PXD101, Beleodaq®) have been approved for the treatment of hematologic tumors. In clinical use as anti-cancer agents (such as vorinostat, panobinostat, belinostat, and abexinostat), many HDACIs inhibit a broad spectrum of HDACs, including Class I, II, and IV isoforms. Although these HDACIs have promising efficacy in treating specific tumors, they all exhibit significant toxicity, including fatigue, nausea, vomiting, thrombocytopenia, and neutropenia (3). Thus, increased effort is being directed toward developing selective HDACIs that are tolerated better and cause fewer adverse reactions. This article focuses mainly on the N-hydroxycinnamamide-based HDAC 1/3 dual inhibitors, and this article outlines the anticancer potential of these inhibitors. Since selective HDAC1/3 inhibitors may cause fewer adverse reactions than selective pan-HDACIs and selective Class I inhibitors in clinical settings, further study of their mechanism of anticancer activity and optimization of their structure is warranted.

Keywords: Epigenetic, HDACs, selective HDACIs, HDAC1/3 selective inhibitors, anti-cancer agent

Histone deacetylases (HDACs) have attracted a great deal of interest as anticancer drug targets, and many HDAC inhibitors (HDACIs) have displayed clinical efficacy in treating specific tumors. However, all of these agents have significant toxicity, including fatigue, nausea, vomiting, thrombocytopenia, and neutropenia. Thus, increased effort is being directed toward developing selective HDACIs that are tolerated better and cause fewer adverse reactions. This article focuses mainly on the N-hydroxycinnamamide-based HDAC 1/3 dual inhibitors, and this article outlines the anticancer potential of these inhibitors. Since selective HDAC1/3 inhibitors may cause fewer adverse reactions than selective pan-HDACIs and selective Class I inhibitors in clinical settings, further study of their mechanism of anticancer activity and optimization of their structure is warranted.

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authors’ laboratory. This work represents the first report of such selective inhibitors with oral activity. The representative compound 11r had low nanomolar IC\textsubscript{50} values in response to HDAC1 (11.8 nM) and HDAC3 (3.9 nM) and micromolar or submicromolar IC\textsubscript{50} values in response to other HDACs such as HDAC2, HDAC4, HDAC6, HDA8, and HDAC11 (Figure 3). Both \textit{in vitro} and \textit{in vivo} studies demonstrated that these HDAC1/3 dual inhibitors could help treat cancer. \textit{In vitro}, some of the selective inhibitors block the proliferation of cancer cell lines, including those of solid and hematologic tumor cells, better than pan-HDAC1 vorinostat (Table 1). Western blot analysis of procaspase 3 and flow cytometry analysis revealed that the potent HDAC1/3 dual selective inhibitors significantly induce cancer cell apoptosis in a time-dependent and dose-dependent manner.
manner. An In vivo study in a subcutaneous U937 xenograft model revealed that the most potent and selective compound was 11r, which inhibited tumor growth 55.1% (Table 2). Moreover, mice treated with 11r had no significant weight loss and no signs of liver or spleen toxicity (I2). More detailed study of their mechanism of anticancer activity and optimization of their structure to improve transcellular permeability and isoform selectivity are underway in this laboratory.

Selective HDAC1/3 inhibitors are selective for HDAC1 and 3 versus HDAC2, so this type of selective inhibitor may offer a better therapeutic approach over pan-HDACs. In addition to their activity against cancer, HDACIs have been studied in the treatment of neurodegenerative disorders, including Huntington’s disease and Friedreich’s ataxia. Thus far, a phase I clinical study of selective Class I HDACI RG2833 for the treatment of Friedreich’s ataxia has begun, and phase II clinical trials of selective SIRT 1 inhibitors to treat Huntington’s disease (HD) have been conducted. Moreover, HDACIs, and particularly hydroxamate-based inhibitors, have surprisingly been found to show synergistic activity with antifungal agents against fungal species at concentrations that are not toxic to the host. One example is HDACI MGCD290, which was discovered by MethyGene. This inhibitor has been found to have activity against fungal pathogens (including azole-resistant yeasts) especially when used in combination with azole antifungals (I3). Human HDACs are related to yeast transcriptional regulators and have similar sequences to yeast Rpd3, Hda1, and Sir2, so an interesting question is whether selective HDACIs have the potential to exhibit such antifungal activity. The anticancer activity of selective HDAC1/3 inhibitors has been verified, but their potential use in other ways, such as treatment of neurodegenerative disorders and fungal infection, has yet to be explored. Thus, HDACIs need to be studied a great deal more.

Acknowledgements

This work was supported by a grant from the National Major Scientific and Technological Projects of Ministry of Science and Technology of China (Grant no. 2011ZX09401-015), a grant from the National Natural Science Foundation of China (Grant no. 21302111, Grant no. 21172134), a grant for projects funded by the China Postdoctoral Science Foundation (Grant no. 2013M540558), a grant from the Special Fund for Innovative Postdoctoral Projects of Shandong Province (Grant No.201303090), a grant from the Independent Innovation Foundation of Shandong University (IIFSDU) (Grant no. 2013GN013), a grant from the US National Cancer Institute of the National Institutes of Health (Award no. R01CA163452), and a grant from the National High-tech R&D Program of China (the “863 Program”) (Grant no. 2014AAA020523).

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(Received September 22, 2014; Revised October 14, 2014; Accepted October 16, 2014)