Novel Histone Deacetylase 8 Ligands without a Bidentate Zinc Chelating Group

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Technology description

This novel ligand excludes hydroxamic acid and inhibits activity of HDAC8. The probes are coupled with photoreactive groups for analysis of novel inhibitor binding sites, allowing optimization of inhibitor design.

HDACs play global roles in the regulation of gene transcription, cell growth, survival and proliferation, and require assembly into larger protein complexes for activity.

Recent studies have shown that their aberrant expression or activity can lead to the development of cancer.

This has led to a rapidly growing interest in the development of HDAC inhibitors as anticancer agents for the treatment of solid and hematological malignancies.

Apart from oncology, HDAC inhibitors are also being evaluated in other indications, such as Huntington's disease or Friedreich's ataxia, because in both cases transcriptional dysregulation has been shown to be a common major pathology.

Currently, there are several inhibitors advancing through clinical trials, most of which inhibit multiple HDAC isoforms.

While promising, these compounds have exhibited toxicities in the clinic that might limit their potential, particularly in solid tumors.

The vast majority of HDAC inhibitors contin a zinc chelating group as an essential part of their binding affinity, which is typically a hydroxamic acid functionality. These are known to undergo rapid hydrolyzation, have low metabolic stability, are poorly absorbed in vivo, and are postulized to be somewhat toxic.

University of Illinois at Chicago scientists developed novel chemical compounds, without the hydroxamic acid moiety, that inhibit the activity of HDAC8. Knockdown experiments of selective HDAC isoforms have revealed that HDAC8 is essential for cell survival, making it an ideal target for cancer therapy.

In addition to their inhibitory activity, these probes were also coupled with photoreactive groups for the discovery and analysis of novel inhibitor binding sites, thus allowing for the optimization of the inhibitor design.

It was discovered that the ligands attach at a secondary binding site in an "upside-down" fashion, which provides valuable insight into how non-hydroxamic acid compounds could be designed to increase inhibition.

Application area

Probes for study of HDAC binding affinities and isoform configuration
Drug design of HDAC8 inhibitors without hydroxamic acid groups

Advantages

HDAC8 inhibition at micromolar concentrations
The toxicity of the inhibitor is expected to be lower than the currently existing HDAC inhibitors
The inhibitor is metabolically more stable than the currently existing HDAC inhibitors

Institution

University of Illinois, Chicago

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com