Exprorative Study for Isoform-selective Histone Deacetylase Inhibitors

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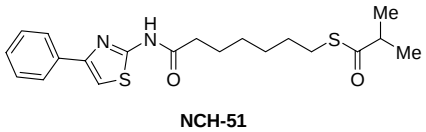
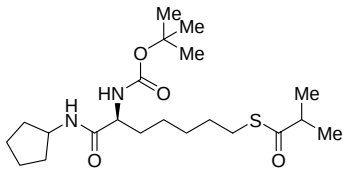
Histone deacetylases (HDACs) catalyze the deacetylation of the acetylated lysine residues of histones and non-histone proteins, and are involved in various fundamental life phenomena, such as gene expression and cell cycle progression. Thus far, eleven HDACs (HDAC1–11) have been identified, but the functions of the HDAC isoforms have not yet been fully understood. In addition, some of the HDAC isoforms have been suggested to be associated with various disease states, including cancer and neurodegenerative disorders. Therefore, isoform-selective HDAC inhibitors are of great interest, not only as tools for probing the biological functions of the isoforms, but also as candidate therapeutic agents with few side effects.[1] With a back ground like that, we initiated research programs to find isoform-selective HDAC inhibitors.

Although a number of structurally diverse HDAC inhibitors have been identified, including trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA), most hydroxamate HDAC inhibitors such as TSA and SAHA inhibit all of the HDAC isoforms. We hypothesized that the non-isoform selectivity of hydroxamate HDAC inhibitors is due to their high ability to coordinate the zinc ion in the active site of HDACs, and the discovery of non-hydroxamate HDAC inhibitors could lead to the identification of isoform-selective HDAC inhibitors. We designed non-hydroxamate HDAC inhibitors based on the three dimensional structure of the enzyme and on the proposed catalytic mechanism of HDACs, and found novel zinc-binding groups such as thiol as a replacement of hydroxamic acid.[2] We then designed isoform-selective HDAC inhibitors using the homology model of HDAC6, one of the HDAC isoforms, and found HDAC6-insensitive inhibitor NCH-51 and HDAC6-selective inhibitor NCT-10.[3]

Furthermore, we elucidated the functions of HDAC6 by chemical genetic approach using NCT-51 and NCT-10. Specifically, we found that HDAC6 is involved in the accumulation of reactive oxygen species in multiple myeloma cells,[4] and HDAC6 is responsible for the proliferation of breast cancer cells.[5] These results also suggested the possibility of isoform-selective HDAC inhibitors as therapeutic agents.



NCH-51



NCT-10

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<References>

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