LASSBio-1911: A new potent histone deacetylase 6/8 dual inhibitor.

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Abstract

Herein we describe a novel class of *N*-acylhydrazone (NAH) derivatives that act as histone deacetylase (HDAC) 6/8 dual inhibitors. LASSBio-1911 was the most potent compound. It inhibits selectively HDAC6/8 in the nanomolar range.

Introduction

There are two families of enzymes that regulate histone acetylation pattern: histone acetyltransferases (HATs) and histone deacetylases (HDACs). The balance between the acetylation and deacetylation of histones affects the structure of chromatin.[1] Some HDACs regulate the function of non-histone proteins, e.g., cytoplasmic proteins and transcription factors. HDACs have been identified as remarkable drug targets in a novel therapeutic approach for the treatment of cancer and related diseases because HDAC inhibition results in the growth arrest, differentiation and apoptosis of many transformed cells.[1,2]

This work describes the structural design, synthesis, *in vitro* pharmacological profile, and molecular modeling of a novel class of *N*-acylhydrazone (NAH) derivatives that act as HDAC 6/8 dual inhibitors.

Results and Discussion

The compounds were designed based on the structure of trichostatin A (TSA) (**1**). The classical bioisosterism was used as the primary molecular modification strategy. We exploited the *N*-acylhydrazone subunit (NAH) for the design of new analogues. We replaced the unsaturated region conjugated to the hydroxamic acid for an interphenylene linker (Figure 1).

The compounds were synthetized using a convergent route. We applied Yamada esterification, hydrazinolysis reaction and a reaction of condensation for the synthesis of the first derivatives. For compounds with the methyl group in the R_1, it was necessary to use protection and deprotection of the amino portion of the hydrazide.

In the biochemical evaluation, carboxylic acid and ester compounds were not active at the concentrations used.

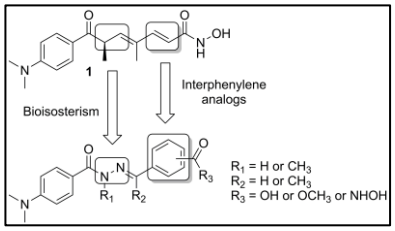

Figure 1 – Structural design of the NAH HDACi.

For the hydroxamic acids, the data for HDAC1, 2, 6 and 8 is presented below.

Table 1 - Inhibitory profile of NAH derivatives

	IC_{50} (μM)			
LASSBio-	HDAC1	HDAC2	HDAC6	HDAC8
TSA	0.0085	0.052	0.009	0.36
1908	>10	>10	2.5	2.0
1909	>3	>3	0.027	0.13
1910	>10	>10	0.39	2.2
1911	>3	>3	0.015	0.23
1935	>3	>3	0.056	0.11
1936	>3	>3	0.097	0.054

Both compounds presented here were selective for HDAC6 and HDAC8, LASSBio-1911 was the most potent with IC_{50} values in the low nanomolar range. LASSBio-1911 induced tubulin acetylation in tumor cell lines and also affected the cell migration by modulation of HDAC6. Cell assays showed that LASSBio-1911 induced cell cycle arrest.

Molecular modeling studies showed that LASSBio-1911 interacts with HDAC6 and HDAC8 in a very similar way.

Conclusions

We used medicinal chemistry strategies for molecular modification and we identified LASSBio-1911, a potent and selective HDAC6/8 dual inhibitor with potency in the nanomolar range. It increases the acetylation of α-tubulin and affects the cell migration. It also induces cell cycle arrest.

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