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Optimization of a series of potent and selective ketone histone deacetylase inhibitors

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ABSTRACT

Histone deacetylase (HDAC) inhibitors offer a promising strategy for cancer therapy and the first generation HDAC inhibitors are currently in the clinic. Herein we describe the optimization of a series of ketone small molecule HDAC inhibitors leading to potent and selective class I HDAC inhibitors with good dog PK.

Histone deacetylase (HDAC) and histone acetyltransferase (HAT) are nuclear enzymes involved in regulating gene expression.[1] The HDAC enzyme family, of which eleven isoforms belonging to classes I, II and IV are known, catalyzes deacetylation of the ε-amino group of lysine residues located near the N-terminus of nucleosome histone proteins. Deacetylated histones acquire a net positive charge that interacts strongly with the negatively charged DNA, thereby condensing the chromatin and restricting accessibility to transcription factors, and ultimately changing gene expression.[2] In cancer the acetylation status of these histone tails is aberrantly regulated and many recent studies have shown that HDAC inhibition leads to anticancer effects, as a result of inhibiting cell growth and inducing apoptosis, as well as causing differentiation and inhibition of angiogenesis. Hence, HDAC inhibition represents a novel approach to cancer chemotherapy,[3] and indeed vorinostat (**1**) (Zolinza®, formerly known as SAHA) has been approved for the treatment of the cutaneous T-cell lymphoma (CTCL),[4] while several other HDAC inhibitors (HDACi) along with vorinostat, are in clinical trials showing efficacy in patient with hematological and solid malignancies.[5] Known HDACi's (Fig. 1) cover a wide cross-section of structures[6] including: hydroxamic acids (typically broad-spectrum HDACi) such as **1**,[7] **2**,[8] and **3**[9] as well as aminobenzamides, for instance **4**[10] and **7**[11] together with their *bis*-aryl derivatives recently disclosed as selective HDAC 1 and 2 inhibitors such as **5**.[12] Other classes include short chain fatty acids like **6**[13] and cyclic peptides such as **8**[14] and **9**.[15]

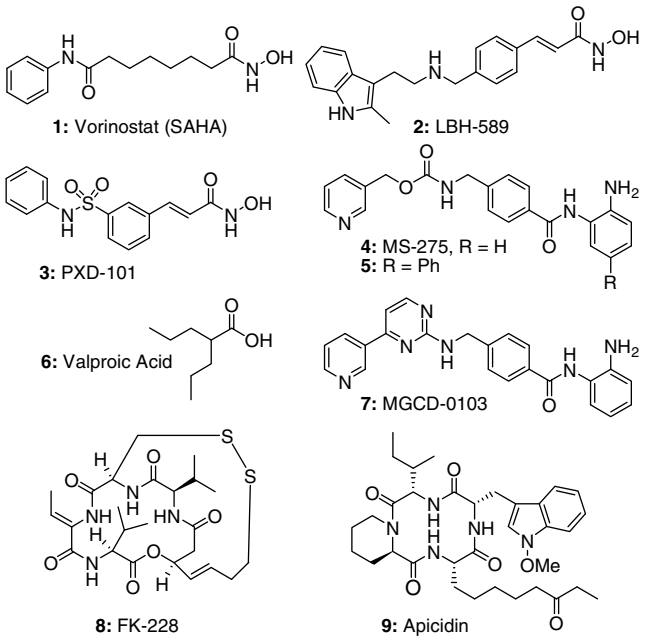

Figure 1. Known HDAC inhibitor.

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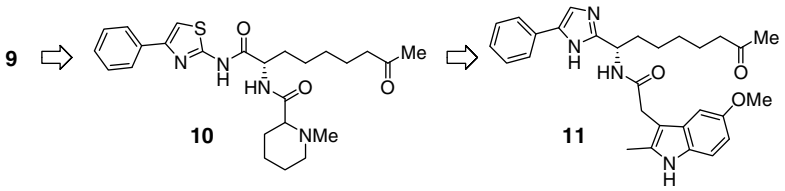


Entry	HDAC1 IC_{50} (nM)	PRO (HeLa) IC_{50} (nM)
9	44	290
10	55	430
11	59	880

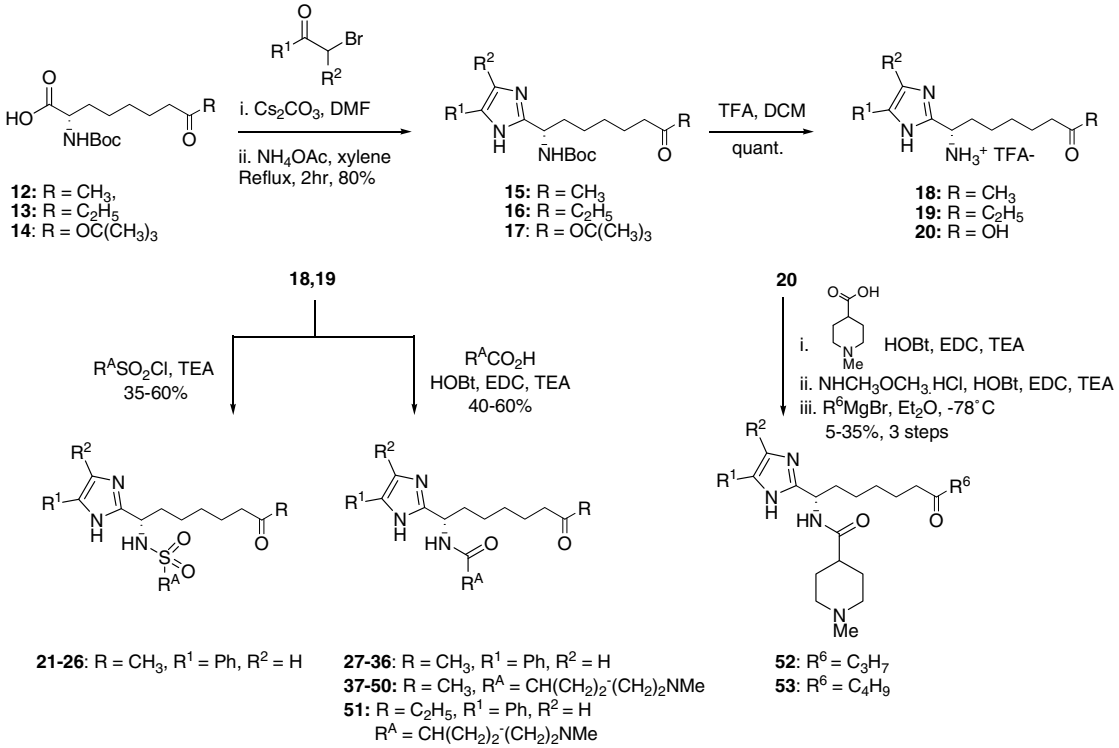
Figure 2. Development of a series of small molecule alkyl ketone HDACi's and the identification of lead **11**. [16]

Recently we have reported the discovery of a structurally novel series of HDAC inhibitors based on the natural compound Apicidin.[16] This natural product contains the unusual ethyl ketone as a zinc binding group (ZBG) yet it is a potent HDAC1 inhibitor (IC_{50} = 44 nM) and displays good anti-proliferative activity (HeLa cells IC_{50} = 290 nM). A related series of simplified acyclic derivatives was identified and optimized to potent and selective HDAC inhibitors such as **10** showing good enzymatic activity against HDAC1 (IC_{50} = 55 nM) and submicromolar activity in the anti-proliferative assay (HeLa cells IC_{50} = 430 nM) (Fig. 2). Unfortunately the heterocyclic acylamino bond was shown to be unstable in rodent plasma, and SAR studies were conducted to identify a replacement to this labile bond by a suitable bioisostere, culminating with the identification of imidazole derivatives exemplified by **11**. [16] Compound **11** displays class I HDAC subtype selectivity and levels of cellular activity in different cancer cell lines comparable to existing clinical candidates. Furthermore in an in vivo efficacy study **11** was shown to cause tumour growth inhibition in a colon HCT-116 carcinoma xenograft model comparable to that achieved with vorinostat and MS-275; to our knowledge this is the first example of an unactivated small molecule alkyl ketone HDACi to be efficacious in vivo. Unfortunately **11** was highly cleared in rats (Cl = 80 mL/min/kg, Rat microsomes Cl_{int} = >300 μL/min/mg) and showed only modest oral bioavailability (F = 15%).

Encouraged by these results we herein describe the further development of this novel class of HDACi and report our work optimizing enzymatic and anti-proliferative activities, together with the efforts to address pharmacokinetic liabilities.

Guided by X-ray crystallographic analysis of a related hydroxamic acid inhibitor bound to HDAC8,[17] SAR investigations focused primarily on the optimisation of the two surface recognition domains, the imidazole substituent and the amino capping group.

The synthesis of these derivatives starts from the readily prepared α-amino acid derivatives **12, 13** (scheme 1) which were first alkylated with the suitable α-bromo ketone and then cyclized to the corresponding imidazoles in refluxing xylene in the presence of a large excess of NH_4OAc. Deprotection and standard coupling conditions yielded either the desired amides **27–51** or the corresponding sulfonamides **21–26**. A small exploration of the ZBG was also conduced starting from the (2*S*)-8-*tert*-butoxy-2-[(*tert*-butoxycarbonyl)amino]-8-oxooctanoic acid **14**. Cyclization as previously yielded the imidazole intermediate **17** which was fully deprotected by treatment with TFA. The resulting amino acid **20** was then coupled with 1-methylpiperidine-4-carboxylic acid and the acid moiety converted into the Weinreb amide. Reaction with the corresponding Grignard reagent provided the homologated *n*-propyl and *n*-butyl derivatives **52** and **53**.



Scheme 1. Synthesis of compounds **21–53**.