Discovery of a Potent Class I Selective Ketone Histone Deacetylase Inhibitor with Antitumor Activity in Vivo and Optimized Pharmacokinetic Properties

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Abstract: The optimization of a potent, class I selective ketone HDAC inhibitor is shown. It possesses optimized pharmacokinetic properties in preclinical species, has a clean off-target profile, and is negative in a microbial mutagenicity (Ames) test. In a mouse xenograft model it shows efficacy comparable to that of vorinostat at a 10-fold reduced dose.

In the nucleus of eukaryotic cells DNA is tightly packed around nucleosomes composed of histone proteins whose N-terminal tails are subject to a number of modifications like acetylation, methylation, phosphorylation, and others.¹ Histone deacetylases (HDACs^{*a*}) and histone acetyl transferases (HATs) are the two counteracting key enzyme families involved in the regulation of the acetylation status of histone tails (and other non-histone target proteins). The HDAC mediated deacetylation of lysine residues enforces ionic interactions with the negatively charged DNA backbone. This leads to a more condensed form of chromatin that is inaccessible to the transcription machinery. On the contrary, the action of HATs leads to a more relaxed form of chromatin, favoring transcription.²

There are four classes of histone deacetylases. Classes I, II, and IV enzymes possess a zinc ion in their active site and consist of 11 isoforms, whereas class III deacetylases (often referred to as sirtuins) are NAD⁺ dependent enzymes. Many of the class I enzymes (HDACs 1, 2, 3, 8) are preferentially located in the nucleus where they are associated in larger complexes that specifically mediate their catalytic activity. Class II enzymes (HDACs 4, 5, 6, 7, 9 10) may localize in the cytosol, and some of these proteins were shown to shuttle between the nucleus and the cytoplasm in response to external stimuli. HDAC 11 is the only member of class IV.^{3,4}

In malignant cells HDACs are overexpressed, mutated, or aberrantly recruited by oncoproteins, causing hypoacetylation of histones leading to transcriptional repression. Upon the action of HDAC inhibitors (HDACi), the balance in the acetylation status is restored and mostly genes involved in apoptosis, cell cycle checkpoints (G1/S, G2/M), and cellular differentiation are activated. Moreover, a growing number of non-histone target proteins important in the regulation of apoptosis (p53), mitosis (α -tubulin), and cellular migration have been identified, putting



Figure 1. Clinically advanced HDAC inhibitors.

into evidence the ability of HDACi to induce cell death of transformed cells by multiple pathways.⁵

While the precise mechanism of how HDACi exert their anticancer effect remains to be fully elucidated, this new class of chemotherapeutics has demonstrated potent anticancer activities in preclinical and clinical studies.⁶ Vorinostat (1, Figure 1), belonging to the class of hydroxamic acid inhibitors, has been approved by the FDA for the treatment of advanced cutaneous T-cell lymphoma.^{7,8} A number of other compounds are in phase II clinical trials for the treatment of hematological and solid tumors, e.g., **3** (MS-275)⁹ and **6** (MGCD-0103),¹⁰ both belonging to the class of aminobenzamides, **7** (romidepsin, FK228),¹¹ a natural product, and **2** (PXD-101)¹² and **5** (LBH-589),¹³ both hydroxamic acids (Figure 1).⁶

The search for a second generation inhibitor remains an important activity in the field of HDACi, with the ultimate goal being an improved therapeutic window in man. Many hydroxamic acids are poorly selective and show activity against classes I and II enzyme isoforms. Aminobenzamides like 3 and 6 show improved selectivity for HDACs 1, 2, 3, and recently biaryl analogues like 4 (Figure 1) have been reported to have further increased selectivity for HDACs 1 and $2^{.14-17}$ For the class I isoforms the correlation between inhibition and antitumor effect is well established. Therefore, a class I selective inhibitor would be desirable. Compound 1 has antiproliferative activity against cancer cells with an IC₅₀ in the low micromolar range and suffers from a relatively short half-life in man (high plasma $C_{\text{max}}/C_{\text{trough}}$ ratio).¹⁸ A more potent compound with a longer half-life and a smaller plasma $C_{\text{max}}/C_{\text{trough}}$ ratio when dosed orally would be desirable to improve the overall therapeutic window.

Previously we have described how our efforts to identify second generation HDACi started from apicidin (**8**, Figure 2).¹⁹ This cyclic tetrapeptide contains an octanyl ketone chain, which is believed to chelate the zinc ion present in the active site. A novel series of potent low molecular weight HDACi containing the L-Aoda amino acid present in **8** was identified and subsequently transformed into a related series of imidazole containing compounds like **9**, which displays activity in vivo albeit with poor PK properties.^{14,20} Optimization of this new class of compounds has resulted in structures like **10** with improved potency. Although **10** displayed a good PK profile in dogs, it suffered from a high clearance in rats. The related ethyl ketone analogue **11** has an 80-fold reduced activity on HDAC

^{*} To whom correspondence should be addressed. Phone: (+39) 0691093334. Fax: (+39) 0691093654. E-mail: olaf_kinzel@merck.com. ^{*a*} Abbreviations: HAT, histone acetyl transferases; HDAC, histone deacetylases; CYP, cytochrome P450; PK, pharmacokinetic.



Figure 2. Key transitions steps from 8 to imidazole HDACi 9 and 10/11.

6 compared to **10** and is slightly more active against HeLa cells in the proliferation assay (Table 1).²¹

Herein we describe the successful further optimization of these inhibitors culminating in the identification of a potent and HDAC class I selective alkyl ketone HDAC inhibitor with optimized pharmacokinetic properties.

In vitro and in vivo investigations of the metabolism of **10** identified the naphthyl group as the metabolic soft spot in rats.²² This finding triggered an intense investigation of the aryl substituent on the imidazole with the objective to identify moieties that would stabilize our inhibitors. On the basis of our previous results, the nature of the pendent basic amino group also contributes to the overall intrinsic stability of the inhibitors. We therefore set out for a focused optimization of both the aryl substituents (\mathbb{R}^1) and the capping group (\mathbb{R}^2) starting from lead **11**.

The synthesis for most of our compounds followed the route described previously (Scheme 1).¹⁴ Briefly, esterification of N-Boc-protected amino acid 12 with chloromethyl ketones (prepared in two steps from the corresponding carboxylic acids) was followed by cyclization of the intermediate ketoesters by heating for 5 min at 150 °C (microwave oven) in o-xylene in the presence of excess ammonium acetate to afford N-Boc protected imidazole intermediates (14a-f). Deprotection of the amino function and standard derivatization furnished the desired final products (15-22, 24). Alternatively, in cases where esterification via alkylation with halomethyl ketones was unsuccessful, the final compounds were prepared from advanced intermediate 25 by Suzuki-Miyaura cross-coupling and imidazole deprotection (Scheme 2).²³ On a larger scale, compound 32 was prepared via the route shown in Scheme 3. Ortholithiation of 2-methoxyquinoline and reaction with TBSprotected hydroxyacetaldehyde gave alcohol 28, which was oxidized and deprotected under mild conditions to afford hydroxymethyl ketone 29 in good yield. This intermediate was coupled to amino acid 12 using EDC, giving rise to a keto ester intermediate 30 which was treated with excess of ammonium acetate in refluxing toluene to obtain imidazole intermediate 31. The azetidine-3-carboxamide moiety was installed by coupling with N-Boc-azetidine-3-carboxylic acid, Boc-removal, and reductive alkylation. Direct amide coupling with N-methylazetidine-3-carboxylic acid gave low yields.

With the aim to improve the metabolic stability in rats and to maintain the good activity of analogues containing a naphthyl group like 11 we first explored heteroatom containing aryl groups like quinoline isomers. The results are shown in Table 1 (15–18). Quinolin-2-yl analogue 15 loses 2-fold in activity

Table 1. Activity on HDAC 1, Antiproliferative Activity against HeLa

 Cells, Intrinsic Metabolic Stability, in Vivo Rat Clearance



N°	\mathbb{R}^1	H R²	IDAC 1 IC50/ nM ^a	HeL a CC50/ nM ^a	Cl _{int} (r/d/h) ^b µL/min/m g	Cl ^c rat
10 d		``\N	11	300	194	$\frac{13}{3}$
11		**	12	210	>200 (rat)	-
15	N	19	22	480	110, 9, 12	$15 \\ 5$
16		"	8	22	210, 18, 29	-
17		"	4	250	510, 24, 49	-
18	N	н	2	200	98, 23, 12	-
19	OMe	H	30	770	36, 5, 10	36
20	n	-N.	51	500	38, 6, 15	59
21	n	N	17	390	190, 170, 140	
22	"	`□ _N	162	970	15, 9, 16	20
23		п	39	1200	13, 3, <1	
24			8	430	27, 20, 19	-
26	N F	"	8	190	34, 28, 18	-
32	N OMe	"	13	135	29, 29, 31	1 9

^{*a*} IC₅₀ and CC₅₀ values are averaged from multiple determinations $(n \ge 2)$. Standard deviations are <30% of the mean. ^{*b*} r = rat; d = dog; h = human. ^{*c*} Units: (mL/min)/kg. ^{*d*} Methyl ketone analogue.

with respect to **11** but is more stable in rat liver microsomes. Unfortunately, its in vivo clearance in rats remains very high (Cl = 155 (mL/min)/kg). Isoquinolin-2-yl analogue **16** is 10-fold more potent than **21** in the proliferation assay but has a similar high microsomal turnover. Even less stable is the quinolin-3-yl analogue **17**. Quinolin-6-yl analogue **18** shows a similar stability in rat liver microsomes as **15** and was not tested in vivo.

After the initial exploration of quinoline isomers our attention turned to quinolines with additional substituents or naphthyl replacements containing two heteroatoms.

The 4-methoxy-quinolin-2-yl analogue **19** is largely stabilized in liver microsomes from all three tested species compared to **11** and **15**. This improvement is reflected in reduced clearance in vivo in rats (Cl = 36 (mL/min)/kg). Despite this encouraging Scheme 1^a



^{*a*} Reagents and conditions: (a) (i) Cs₂CO₃, EtOH (ii) **13a–f**, DMF, (iii) *o*-xylene, NH₄OAc, 150 °C, 5 min, microwave; (b) DCM, TFA; (c) EDC-HCl, HOBt, Et₃N, DMF, R²CO₂H.

Scheme 2^{*a*}



^{*a*} Reagents and conditions: (a) R¹B(OH)₂, *S*-Phos, Pd(OAc)₂, K₃PO₄, 1-butanol, 80 °C; (b) TFA.

Scheme 3^{*a*}



^{*a*} Reagents and conditions: (a) mesityllithium, TBSOCH₂CHO, THF, 0 °C; (b) DMP, DCM; (c) AcOH/ H₂O/ THF, 3:1:1; (d) EDC-HCl, HOBt, DMAP, DMF, **12**; (e) toluene, NH₄OAc, reflux; (f) DCM, TFA; (g) EDC-HCl, HOBt, DMF, *N*-Boc-azetidine-3-carboxylic acid; (h) H₂CO, NaOAc, MeOH, H₂O, NaBH₃CN.

result, the activity of **19** was not deemed sufficient ($CC_{50} =$ 770 nM) and further SAR at R² was explored with the aim to improve enzymatic and cellular activity. The *N*,*N*-dimethylaminoethyl analogue **20** is slightly more active in the proliferation assay but displays a higher clearance in rats (Cl = 59 (mL/min)/kg). Compound **21** has a 2-fold increased activity but unfortunately is unstable in liver microsomes of all species. Analogue **22** bearing a *N*-methylazetidin-3-yl as R² captured our interest because of its increased stability in liver microsomes and in rats (Cl = 20 (mL/min)/kg). At this point we decided to turn our attention to further SAR exploration of R¹, keeping the *N*-methylazetidin-3-yl constant.

The quinoxalin-6-yl analogue **23** demonstrates a 4-fold higher enzyme activity compared to **22** and very good stability in liver microsomes. Unfortunately, activity in the proliferation assay remains in the micromolar range. Quinoxalin-2-yl analogue **24** exhibits a further 5-fold increase in activity against HDAC 1

Table 2. Activity of **32**, **1**, and **3** against HDAC Isoforms (IC₅₀, nM) and Cancer Cell Lines (CC_{50} , nM)^{*a*}

	(30,)		
isoform	32	1	3
HDAC 1	13	30	120
HDAC 2	18	82	250
HDAC 3	12	57	400
HDAC 4^{b}	>10 µM	>10 µM	>10 µM
HDAC 5	$>1 \mu M$	$>10 \ \mu M$	$>10 \ \mu M$
HDAC 6	680	43	>10 µM
HDAC 7	>10 µM	>10 µM	$>10 \ \mu M$
HDAC 8	$>10 \ \mu M$	1700	$>10 \ \mu M$
cell line	32	1	3
cervical HeLa	135	460	1800
colon HCT-116	220	1000	700
lung A549	490	1800	1200
kidney G401	370	1000	1300
ovarian A2780	740	2600	3000
breast MCF-7	750	3000	nd
leukemia U937	240	1050	nd

^{*a*} IC₅₀ and CC₅₀ values are averaged from multiple determinations $(n \ge 2)$, standard deviations are <30% of the mean; ^{*b*} refers to HDAC 4 wt as described in ref.¹⁴

Table 3. PK Profile of 32

	rat	dog
Cl ((mL/min)/kg)	19	4
Vd _{ss} (L/kg)	7.9	3.5
$t_{1/2}$ (h)	7	14
$F(\%)^a$	73	31

^a Dosed as L-tartrate salt.

and a 3-fold improvement in the proliferation assay compared to **22**, maintaining good stability in liver microsomes. A further increase in antiproliferative activity is obtained with the 2-fluoroquinolin-3-yl analogue **26** ($CC_{50} = 190$ nM), and subsequent replacement of the fluoro substituent by a methoxy group yields **32** with a CC_{50} of 135 nM, good liver microsome stability, and a low clearance when dosed in rats.

The 2-methoxyquinoline **32** was profiled on the various HDAC isoforms, with **1** and **3** (Table 2). The ketone **32** has low nanomolar IC₅₀ values against the HDAC class I isoforms 1, 2, and 3 and is inactive on all other tested isoforms with the exception of HDAC 6 where there is a 30-fold selectivity. In comparison, **1** displays weaker activity on HDACs 1-3 and high activity on HDAC 6 (IC₅₀ = 43 nM). It also displays some activity against HDAC 8. Compound **3** shows a similar degree of selectivity for HDACs 1-3 as **32** but is 10- to 30-fold less active (Table 2).

In proliferation assays against a wide panel of cancer cell lines 32 proved to be 3- to 4-fold more active compared to 1 and 2- to 10-fold more active than 3 (Table 2).

The pharmacokinetic properties of **32** as the L-tartrate were determined in rats and dogs (Table 3). In both species low clearance and long terminal half-life are observed. The oral bioavailability is excellent in rats and acceptable in dogs. This is noteworthy, considering the presence of the long and very flexible alkyl ketone chain (>7 freely rotatable bonds). After oral doses to rats (3 mg/kg) and dogs (2 mg/kg) good levels of **32** (>100 nM) are detected in plasma out to 24 h. The compound also displays excellent solubility of 13 mg/mL in buffered aqueous solution at pH 4.1, suggesting that **32** is suitable both for iv and oral dosing in man.

In a preliminary efficacy study in a subcutaneous HCT116 xenograft mouse model **32** displays comparable antitumor activity to **1** when dosed 5 days per week at the maximum tolerated dose (MTD). This activity of **32** is observed at $\frac{1}{10}$ of



Figure 3. Human HCT116 colon cancer xenograft model in nude mice (10 per group). Compounds: **32** (\blacktriangle) 10 mg/kg, **1** (\times) 100 mg/kg, and vehicle (\Box), administered ip once a day, 5 days per week.

the dose of **1**, and no adverse effects or significant body weight loss is observed (Figure 3).

Counterscreen on a panel of 150 enzymes or receptors (MDS Pharma Services) reveals no significant off-target activities, with **32** displaying at least 100-fold selectivity. No significant CYP3A4 inhibition or induction is found (although weak inhibition of CYP2C9, $IC_{50} = 5.5 \ \mu$ M).

When **32** was dosed via continuous infusion to dogs, no major effect on hemodynamics and cardiac electrical activity was observed with plasma levels reaching 30 μ M. In a microbial mutagenicity test (Ames) **32** is negative.

In summary, starting from lead **11**, optimization of the two capping groups R^1 and R^2 of the inhibitors has led to the identification of **32**, a potent, selective HDACs 1, 2, and 3 inhibitor that has excellent pharmacokinetic properties in preclinical species. The alkyl ketone **32** displays antitumor activity comparable to that of clinical candidates and is devoid of off-target activities.

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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