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Novel HDAC6 isoform selective chiral small molecule histone deacetylase inhibitors

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ABSTRACT

In an effort to identify HDAC isoform selective inhibitors, we designed and synthesized novel, chiral 3,4-dihydroquinoxalin-2(1*H*)-one and piperazine-2,5-dione aryl hydroxamates showing selectivity (up to 40-fold) for human HDAC6 over other class I/IIa HDACs. The observed selectivity and potency (IC_{50} values 10–200 nM against HDAC6) is markedly dependent on the absolute configuration of the chiral moiety, and suggests new possibilities for use of chiral compounds in selective HDAC isoform inhibition.

The reversible hyperacetylation of lysine residues on the *N*-terminal tails of core histone proteins H2A/B, H3, and H4 (correlated with gene activation), and histone hypoacetylation (leading to transcriptional repression), are catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively.[1] The 18 known human HDACs, 11 of which are functionally related Zn^{+2}-dependent amidohydrolases, are grouped into three classes (I, II, and IV). Class I/II HDACs show some structural homology to each other within their catalytic domains, but are structurally distinct from the NAD^{+}-dependent class III HDACs (sirtuins, SIRT1-7).[2] HDAC subtypes 1, 2, 3 and 8 collectively make up class I (HDAC11 is assigned as class IV), and are ubiquitously expressed, predominantly nuclear enzymes. Class II is comprised of six HDAC isoforms, and is itself divided into two subclasses, IIa (HDACs 4, 5, 7 and 9) and IIb (HDAC6 and HDAC10). The IIb subclass enzymes uniquely feature two deacetylase domains, and are primarily cytoplasmic, while class IIa members shuttle between the nucleus and cytoplasm. Furthermore, unlike class I HDACs, class IIa/b enzymes are expressed in a more limited number of cell types. Significantly, class IIb enzyme HDAC6 operates on a variety of substrates other than histone proteins, and is involved in processing Lys40 of the mitotic spindle protein α-tubulin.[3]

It is known that HDAC inhibitors regulate differentiation, proliferation, cell cycle, protein turnover, and apoptosis,[4] and can function as targeted chemotherapeutic agents.[5] Despite the broad structural and chemical spectrum of HDAC inhibitors under clinical development, few show notable or significant specificity for class I versus class II enzymes, or any subtype selectivity within a given class. Perhaps the most selective HDAC inhibitors are benzamides, exemplified by MS275 and its aryl substituted analog (Fig. 1), showing high potency and exclusive class I activity confined primarily to the HDAC 1, 2, 3 subtypes.[6] The prodrug FK228 (depsipeptide/Romidepsin®) also shows this class I selectivity, with no additional subtype selectivity.[6a]

In the realm of hydroxamate-based inhibitors, such levels of selectivity are rarely observed, with most inhibitors tending to be pan class I and II, such as SAHA, LBH589, PXD101, JNJ26481585 and ITF2357.[6a] While limited reports have been published outlining class IIb[7] and HDAC8[8] selectivity, most progress has been made in the area of HDAC6 selectivity. The disclosure of tubacin (Fig. 2), a high molecular weight (>700 D)

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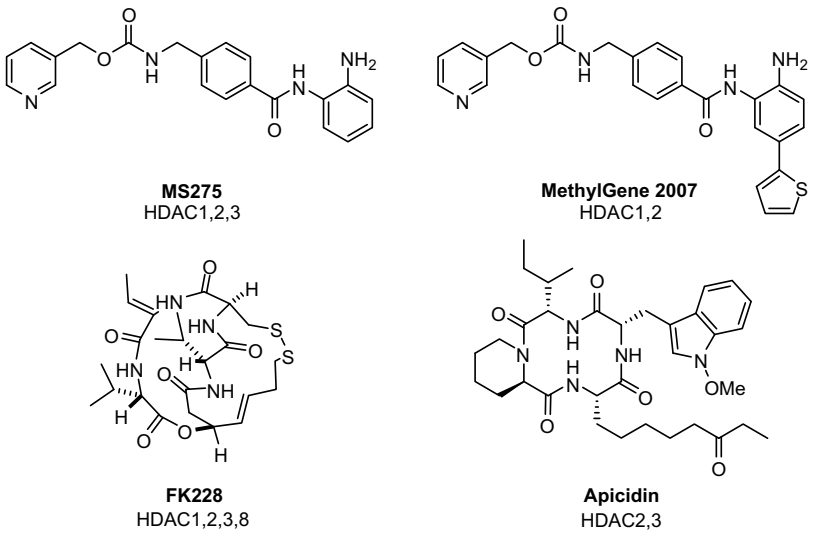


Figure 1. Known potent and selective class I HDAC inhibitors.

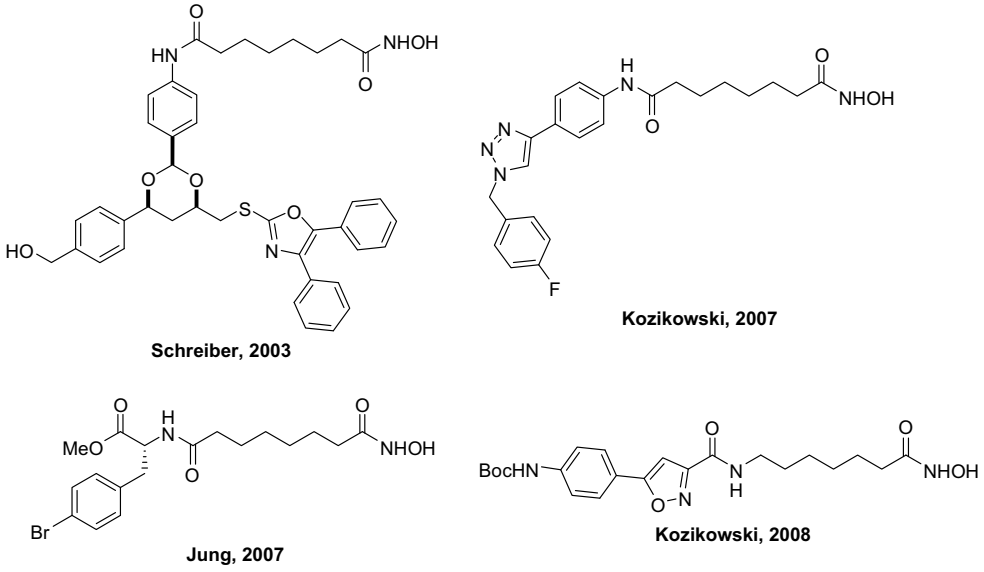


Figure 2. Reported HDAC6 selective inhibitors.

1,3-dioxane containing hydroxamate, by Schreiber and co-workers was the first example of a compound capable of selectively inhibiting class IIb subtype HDAC6, and inducing α-tubulin acetylation.[9] Several years later, Jung et al. described phenylalanine-containing hydroxamates that exhibited activity against HDACs (IC_{50} values typically >0.30 μM), and modest HDAC6 selectivity (5- to 14-fold over HDAC1).[10] More recently, Kozikowski et al. have described potent and HDAC6 selective triazolylphenyl capped hydroxamate inhibitors (HDAC6 IC_{50} = 1.9 nM and 51-fold selectivity over HDAC1),[11] and related phenylisoxazole capped hydroxamates (HDAC6 IC_{50} = 0.002 nM and 210-fold selectivity over HDAC3).[12] In all instances, the inhibitors are suberic acid or lysine-based, relying almost exclusively on this structural feature in order to achieve the observed potencies against the enzyme, and employing the capping moiety (enzyme surface recognition domain) as a presumed selectivity element.

Guided by the documented role of HDAC6 regulation in neuroprotection,[13] we were also interested in the selective inhibition of this HDAC isoform. The possibility of employing a chiral capping moiety to potentially confer this HDAC class/isoform selectivity and potency to an aryl hydroxamate was considered an attractive option given the literature data reported for apicidin (Fig. 1), a macrocyclic tetrapeptide electrophilic ketone HDAC inhibitor showing some HDAC2 and HDAC3 selectivity over HDAC1, HDAC8, and all class II HDACs, with potencies in the nM range.[14] Work by Yoshida and co-workers involving the hybridization of hydroxamate-based inhibitors with these cyclic tetrapeptide class structures, termed CHAPs, also served to demonstrate that the surface recognition domain of the compound affects not only potency, but selectivity as well. Several of the CHAPs synthesized showed low nM potencies, and exhibited 10- to 90-fold selectivity for HDAC1 over HDAC6.[15] The solvent-exposed periphery of the enzyme's catalytic site, a region showing significant sequence diversity between class I and II HDACs,[9a] can provide a structural rationale for the observed selectivity of apicidin and the CHAPs, and suggests that selectivity for other HDAC isoforms may be achievable by use of a similar strategy involving a chiral, enzyme rim binding pharmacophore.

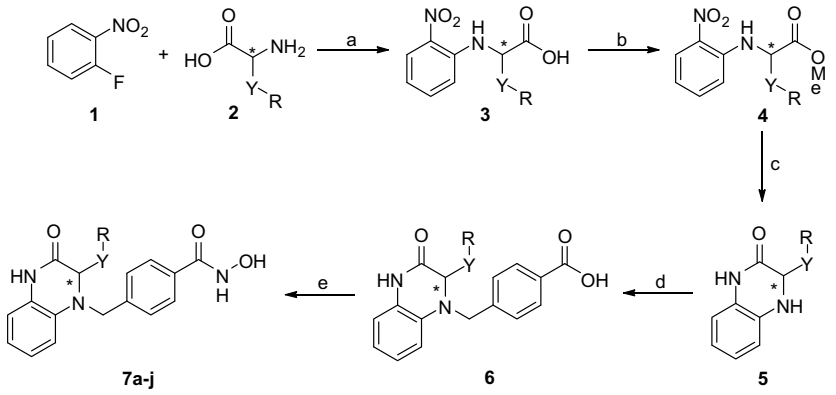
Although the cyclic tetrapeptide capping region of apicidin and the CHAPs is structurally complex, it was anticipated that the significant contribution it makes to rim binding could be replicated effectively in a simplified system employing similar structural elements; principally, the H-bond donor/acceptors and chirality available in the cap's constituent amino acid derived amides, and its' 'space filling' topology. With these elements in mind, it was envisaged that introduction of a chiral component into the capping portion of the novel hydroxamate inhibitors would be most rapidly and efficiently accomplished through the use of commercially available chiral starting materials such as (D)- and (L)-amino acids. To this end, the chosen amino acids could either be appended to a rigidifying aryl moiety to form 3,4-dihydroquinoxalin-2(1*H*)-one caps (Scheme 1), or be incorporated into less rigid piperazine-2,5-dione caps (Scheme 2); a strategy complementary to the use of 1,4-benzodiazepine-2,5-diones and 1,4-benzodiazepines as constrained peptidomimetics for the capping of lysine-based HDAC inhibitors reported by Tranoy-Opalinski et al.[16] and Romanelli et al.[17], respectively. Both types of caps are inherently appealing in terms of their ease of synthesis, and in the different topology and steric bulk accessible through the judicious selection of starting materials. In order to reduce the total number of rotatable bonds in the final inhibitor, it was also established at the outset to employ an aryl linker in the construction of the overall molecular scaffold. Based on extensive observations made in our laboratories, use of an aryl linker was viewed as a viable option, and was not expected to impair the potency of any hydroxamates prepared for this study.

Synthesis of the rigid 3,4-dihydroquinoxalin-2(1*H*)-ones **5** began with the facile S_NAr coupling of glycine or various (D)- and (L)-amino acids to 1-fluoro-2-nitrobenzene **1**, giving rise to the 2-nitrophenylamino acid derivatives **3** (Scheme 1). Subsequent esterification with iodomethane providing intermediates **4** proceeded in essentially quantitative yield, and supplied material requiring no additional purification prior to the next step. Reduction of the nitrophenyl moiety that followed was accompanied by in situ cyclization to form the target 3,4-dihydroquinoxalin-2(1*H*)-ones **5** in high yield. Intermediates **6** were then obtained via reductive amination employing 4-formylbenzoic acid, catalytic dibutyltin dichloride, and phenyl silane as the reductant.[18] Final transformation to the desired hydroxamic acids **7** was performed using the BOP mediated coupling of hydroxylamine hydrochloride. The conditions employed in this step, like in all prior steps, were selected to avoid racemization of the solitary chiral center within the structure. Overall, this five step sequence proved to be efficient, high yielding, and general, allowing access to a diverse set of hydroxamates **7**.

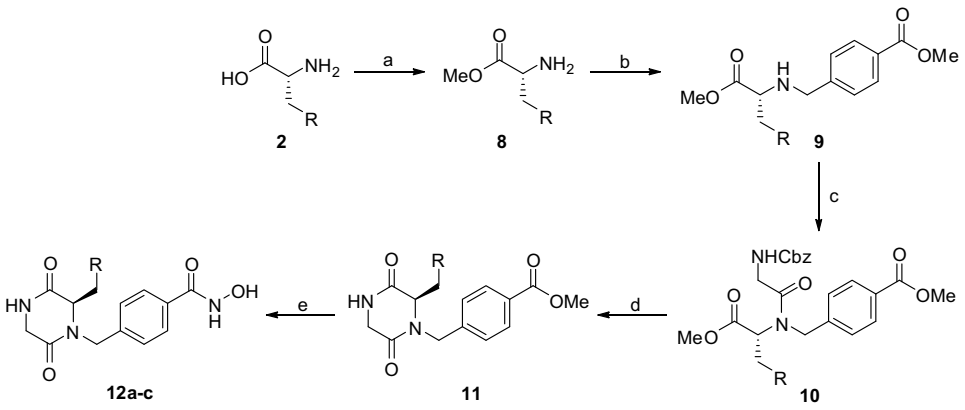
Construction of the less rigid piperazine-2,5-dione caps found in the second series of hydroxamates **12** was initiated with the esterification of several (D)-amino acids, giving rise to building blocks **8** (Scheme 2). Unlike in the previous sequence, subsequent reductive amination using methyl 4-formylbenzoate and sodium borohydride as the reductant was employed for the earlier introduction of the aryl linker moiety, providing the intermediates **9**. Further elaboration through amidation with *N*-Cbz-glycine under either EDCI/HOBt or HATU/DIPEA conditions allowed for access to intermediates **10**. As in the previous synthetic route, it was expected that reductive cleavage of the Cbz protecting group from the glycine fragment using catalytic palladium and hydrogen atmosphere conditions would result in concomitant cyclization to the penultimate intermediates **11**. This strategy did work for the cases where R = phenyl and 3-indole, but failed for the conversion of the substrate with R = 2-thiophene, resulting in partial reduction of the thiophene moiety. In this later case, an alternative strategy relying on HBr/AcOH mediated cleavage of the Cbz group and subsequent high temperature cyclization was used to access that material. Transformation of **11** to the final hydroxamic acids **12** was then effected directly from the methyl esters by means of a mild and general protocol employing aqueous hydroxylamine under basic conditions.

All of the hydroxamate inhibitors in the **7** and **12** scaffold series, along with reference compound (±)-trichostatin (TSA), were initially analyzed for their potency and selectivity against a panel of recombinant human HDACs. This panel was comprised of HDAC1-8 isoforms that had been affinity purified together with their cofactors. The data for HDAC6 (class IIb) and HDAC2 and 8 (chosen as representative class I enzyme subtypes) is collected in Table 1. All other HDAC inhibition values are consistent with the observed trends discussed below, and are thus omitted for purposes of clarity.

On examination, we found that the parent 3,4-dihydroquinoxalin-2(1*H*)-one capped hydroxamate **7a** (which lacks a chiral moiety) shows no appreciable selectivity for any of the class I or II HDACs. Remarkably, however, it's evident that not only is HDAC6 selectivity achievable using some of the *chiral* variants in the **7** scaffold series, but that this selectivity is dependent on the absolute configuration of the chiral centre. For example, while the (*S*) configured hydroxamate **7c** exhibits essentially no selectivity across the entire HDAC panel, the isomeric (*R*) compound **7b** shows a 26-fold selectivity for HDAC6 over HDAC2, and a 53-fold selectivity for HDAC6 over HDAC8. The selectivity of **7b** for HDAC6 with respect to all other members of the HDAC panel (not shown) tended to be comparable, or greater. The isomeric pair **7d/e** also



Scheme 1. Reagents and conditions: (a) K_2CO_3, EtOH/H_2O (5:1), 100 °C, sealed tube, 16 h (>95%); (b) K_2CO_3, MeI, DMF, rt, 16 h (>95%); (c) H_2, 10% Pd/C, MeOH/EtOAc (2:1), rt, 16 h (>80%); (d) 4-formylbenzoic acid, $PhSiH_3$, Bu_2SnCl_2, THF, rt, 16 h (>80%); (e) $NH_2OH{\cdot}HCl$, BOP, TEA, Pyr., rt, 8 h (>50%).



Scheme 2. Reagents and conditions: (a) HCl/MeOH, rt, 16 h (>70%); (b) methyl 4-formylbenzoate, $NaBH_4$, MeOH, rt, 16 h (>40%); (c) *N*-Cbz-glycine with EDCI, HOBt, DMF, rt, 16 h (>80%) for **12a–b** or HATU, DIPEA, DMF, rt, 16 h (54%) for **12c**; (d) 10% Pd/C, MeOH, rt, 16 h (>50%) for **12a–b** or 33% HBr/AcOH, rt, 1 h, followed by 10% NH_4OH/DCM wash and diphenyl ether, 170 °C, sealed tube, 1 h; (95%) for **12c**; (e) NH_2OH, NaOH, THF/MeOH/H_2O, rt, 16 h (>60%).

Table 1
In vitro determination of IC_{50} (μM) values for the inhibition of HDACs 2, 6, and 8 by compounds **7a–j**, **12a–c**, and TSA

Compound	Isomer	Substituent		IC_{50}[a] (μM)			Selectivity index[b]	
		'Y'	'R'	HDAC2	HDAC6	HDAC8	HDAC6 versus HDAC2	HDAC6 versus HDAC8
TSA	—	—	—	0.01	0.02	0.77	1	39
7a	—	H	—	0.56	0.15	0.52	4	3
7b	*R*	CH_2	Ph	0.26	0.01	0.53	26	53
7c	*S*	CH_2	Ph	0.46	0.22	0.21	2	1
7d	*R*	CH_2	2-Thiophene	0.87	0.04	0.69	21	17
7e	*S*	CH_2	2-Thiophene	1.48	0.31	1.19	5	4
7f	*R*	CH_2	3,4-diF-Ph	0.46	0.04	0.42	11	10
7g	*R*	CH_2	4-OH-Ph	0.33	0.01	0.73	41	91
7h	*R*	CH_2	$-CH_2Ph$	0.52	0.01	0.64	40	49
7i	*R*	CH_2	$-(CH_2)_3NHBoc$	1.48	0.04	1.15	34	27
7j	*R*	CH_2	4-*t*BuO-Ph	1.44	0.05	0.25	28	5
12a	*R*	—	Ph	5.54	0.17	2.34	33	14
12b	*R*	—	3-Indole	1.81	0.11	1.21	17	11
12c	*R*	—	2-Thiophene	3.47	0.16	0.44	22	3

[a] Results shown are mean values calculated from experiments conducted in triplicate.
[b] The selectivity index is equivalent to HDAC1 or 8 IC_{50}/HDAC6 IC_{50}.

demonstrates this chirality-induced HDAC6 selectivity, and (*R*) isomeric compounds **7f–j** further maintain the pattern.

This selectivity pattern is also evident with the (*R*) isomers in the piperazine-2,5-dione capped hydroxamate **12** scaffold series. Indeed, when this trend was initially observed after the first several inhibitors in the **7** scaffold series were prepared, only the (*R*) isomers in the **12** scaffold series were synthesized, and produced the expected result. All of the (*R*) isomers in both the **7** and **12** scaffold series show superior HDAC6 over HDAC2 selectivity with respect to TSA. Generally speaking, the nature of the pendent cap substituent 'R' appears to play less of a role in the observed selectivity than the absolute configuration at the chiral centre. Furthermore, the substituent also has little effect on the observed inhibitory potency of the compounds against HDAC6; all of the (*R*) isomers in the **7** scaffold series have activity in the 10–50 nM range (equipotent to TSA), and are more potent as a whole than compounds in the **12** scaffold series, whose values range between 100 and 200 nM.

Substantiation of this data and the associated trend was sought from the measurement of histone H3 acetylation (H3Ac) versus α-tubulin acetylation (TubAc) in cultured human bladder carcinoma T24 cells (Table 2). The T24 cells were treated with escalating doses of inhibitors in the **7** and **12** scaffold series, along with TSA. It was expected that if (*R*) isomers in the chiral **7** and **12** scaffold series were genuinely HDAC6 selective inhibitors, a preferential induction of α-tubulin acetylation (compared to histone H3 acetylation) should be observed.

All of the compounds tested did induce both core histone H3 and α-tubulin acetylation in a dose-dependent manner, with the calculated EC_{50} values suggesting that the latter acetylation is favored (Table 2). The ability of these compounds to preferentially

Table 2
In vitro determination of EC_{50} (μM) values for histone H3 and α-tubulin acetylation by compounds **7a–e**,**i**,**j**, **12a–c**, and TSA

Compound	Isomer	Substituent		EC_{50}[a] (μM)	
		'Y'	'R'	H3Ac	TubAc
TSA	—	—	—	0.01	0.01
7a	—	H	—	3.58	1.01
7b	*R*	CH_2	Ph	0.52	0.04
7c	*S*	CH_2	Ph	1.90	0.32
7d	*R*	CH_2	2-Thiophene	1.22	0.07
7e	*S*	CH_2	2-Thiophene	2.30	0.23
7i	*R*	CH_2	$-(CH_2)_3$ NHBoc	6.75	0.09
7j	*R*	CH_2	4-*t*BuO-Ph	2.75	0.08
12a	*R*	—	Ph	23.0	1.49
12b	*R*	—	3-Indole	12.1	2.87
12c	*R*	—	2-Thiophene	9.00	2.00

[a] Results shown are mean values calculated from experiments conducted in triplicate (in T24 cells).

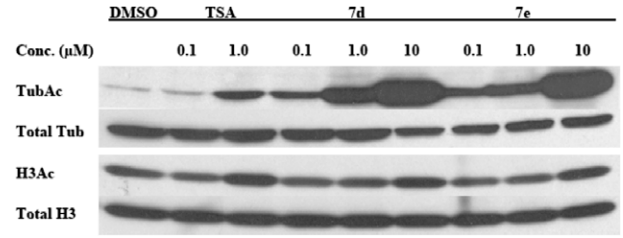


Figure 3. Dose-dependent induction of α-tubulin acetylation versus histone H3 acetylation in vitro in T24 human bladder cancer cells determined for compounds **7d**, **7e** and TSA. Cells were incubated with the HDAC inhibitors at 0.1, 1.0, and 10 μM for 16 h before whole-cell lysates were analyzed for α-tubulin and histone H3 acetylation by SDS–PAGE and Western immunoblot with antibodies specific for either acetylated histone H3 or α-tubulin. Total histone H3 was used to reveal blot loading levels.

induce α-tubulin acetylation in cancer cells is largely correlated with their ability to inhibit HDAC6 selectively in vitro. While TSA and achiral compound **7a**, both non-HDAC6 selective inhibitors, showed no propensity to induce α-tubulin acetylation preferentially over histone H3 acetylation, compounds **7b,c,d,e,i,j** and **12a,b,c** did exhibit this tendency. Once again, the nature of substituent 'R' appears to have little effect on the observed selectivity of the inhibitors, but the chirality of the capping moiety does appear to play a significant role. The less potent and HDAC6 selective (*S*) isomers **7c** and **7e** were, as expected, less efficient α-tubulin acetylation inducers (by about 2-fold versus histone H3 acetylation) than their (*R*) isomer counterparts, **7b** and **7d**, respectively. Furthermore, the overall lower potency of the **12** scaffold series compounds against HDAC6 is reflected in their higher EC_{50} values for α-tubulin acetylation, although their level of selectivity remains significant.

Compound **7i**, a highly selective HDAC6 inhibitor in the in vitro enzyme assay, is a particularly selective promoter of α-tubulin acetylation (75-fold versus histone H3 acetylation), while **7b**, **7d**, **7j**, and **12a** also show relatively high selectivity indices (>13-fold). These results are comparable to the 75-fold selectivity reported for tubacin, but the potencies of the most active α-tubulin acetylation inducers **7b,d,i,j** (with EC_{50} values <100 nM) are far superior to that of tubacin, with an EC_{50} = 2.9 μM.[9c] The data obtained from the cell-based assays are consistent with the results obtained in the in vitro enzyme inhibition assays.

Western blot analysis for isomeric compound pair **7d/e** is illustrated in Figure 3. Clear induction of α-tubulin acetylation is evident with highly selective and potent (*R*) inhibitor **7d** at 1.0 μM, while less selective and potent (*S*) inhibitor **7e** shows a less significant induction effect (comparable to the non-selective control inhibitor TSA). At the compound concentrations investigated in the assay (0.1–10 μM), the Histone H3 acetylation level is seen to vary little with respect to the DMSO control for inhibitors **7d** and **7e**.

In summary, by developing two series of novel aryl hydroxamate HDAC inhibitors incorporating distinct chiral capping motifs, it was determined that in vitro selectivity for HDAC 6 (class IIb) over all other class I and IIa isoforms could be achieved. Moreover, it was established that this selectivity was dependent not only on the presence of the chiral centre, but also on its' absolute configuration. It was also possible to observe a parallel, chiral structure dependent selectivity for α-tubulin acetylation over histone H3 acetylation using in vitro cell-based assays. The majority of compounds effectively induced α-tubulin acetylation at a level comparable to that of tubacin, but were found to be far more potent. Overall, compounds **7b,d,i,j** and **12a** can serve as important tools for further investigations into the selectivity and utility of this class of inhibitors, and to further probe HDAC isoform-specific biological functions or yield insights into HDAC isoform structures.

Supplementary data

Supplementary data associated with this article can be found in U.S. Patent Application 2007/0155730 A1. The enzymatic assays followed the fluorescent signal obtained from the HDAC catalyzed deacetylation of coumarin-labeled lysine. The substrate used for HDAC1, 2, 3, 6, and 8 was Boc-Lys(ε-acetyl)-AMC (Bachem Biosciences Inc.) and Boc-Lys-(ε-trifluormethylacetyl)-AMC (synthesized in-house) for HDAC4, 5, and 7. Recombinant enzymes expressed in baculovirus were used. HDAC1, 2, and 3 were C-terminal FLAG-tagged and HDAC4 (612-1034), HDAC5 (620–1122), HDAC6, HDAC7 (438–915), and HDAC8 are N-terminal His-tagged. The enzymes were incubated with the compounds in assay buffer (25 mM Hepes, pH 8.0, 137 mM NaCl, 1 mM $MgCl_2$ and 2.7 mM KCl) for 10 min at ambient temperature in black 96-well plates. The substrate was added into enzyme-compound mixture and incubated at 37 °C. Reaction was quenched by adding trypsin and TSA to a final concentration of 1 mg/mL and 1 uM, respectively. Fluorescence was measured using a fluorimeter (SPECTRAMAX GeminiXS, Molecular Devices). The 50% inhibitory concentrations (IC_{50}) for inhibitors were determined by analyzing dose-response inhibition curves with GraFit.

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