

# Discovery of SB939, an HDAC inhibitor with a superior preclinical profile

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## Background

- Histone deacetylase (HDAC) inhibitors significantly impact multiple processes involved in tumor progression by inducing epigenetic changes in tumor cells. SAHA (Zolinza™) has demonstrated clinical “proof-of-principle” for this class of compounds.
- Most of the agents currently in clinical trials (Figure 1) have less than optimal pharmaceutical and pharmacokinetic (PK) properties. Our HDAC program aimed to overcome these deficiencies. We have designed and synthesized a series of *N*-hydroxy-1,2-disubstituted-1*H*-benzimidazol-5-yl acrylamides (VII) (Scheme 1) as novel HDAC inhibitors.<sup>1</sup> A representative of the series, SB639 (Figure 2), has demonstrated oral anti-tumor activity in a colon cancer xenograft model.
- Here, we present how our extensive structure-activity relationship (SAR) studies help to fine-tune the drug-like properties of VII and how our integrated drug profiling processes have lead to the discovery of SB939 (Figure 2) with a superior preclinical profile, a potential “best-in-class” HDAC inhibitor.

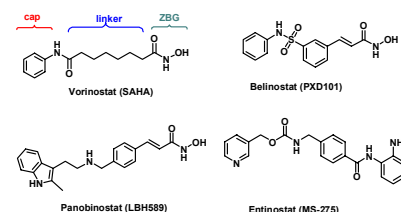


Figure 1. Examples of clinically tested HDAC inhibitors

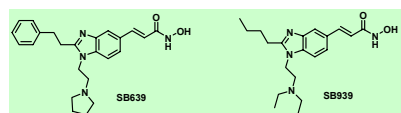


Figure 2. S\*BIO's Benzimidazole-based hydroxamate HDAC inhibitors

## Materials and Methods

- Hydroxamates (VII) were synthesized according to similar protocols established for the SB639 series but with modifications (Scheme 1). A variety of side chains, R<sup>1</sup> (Figure 3) and R<sup>2</sup> (Figure 4) were selected to explore SAR and tune ADME properties. Further modification of R<sup>1</sup> was carried out according to Route D, Scheme 1.
- Compounds with good enzyme, cellular and ADME properties<sup>2</sup> were screened for pharmacological activity in the mouse HCT116 xenograft model. Lead candidates were further evaluated in different xenograft models.
- Biomarker studies on the levels of acH3 (acetylated histone H3) in nude mouse HCT116 tumor tissues confirmed the mechanism of action *in vivo*, and established PK/PD (pharmacodynamic) correlations for evaluation and selection of pre-clinical development candidates.

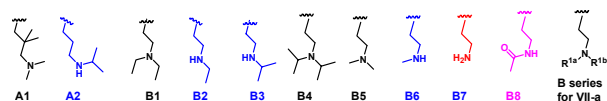


Figure 3. Examples of R<sup>1</sup>

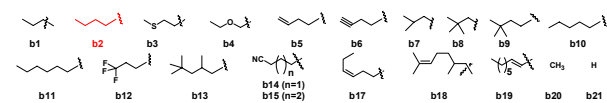
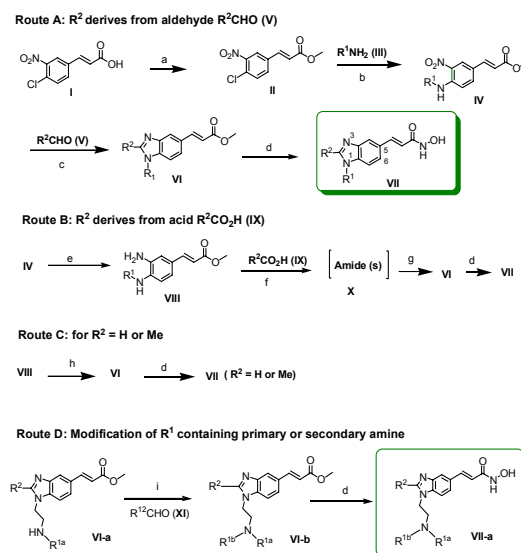


Figure 4. Examples of R<sup>2</sup>



**Scheme 1.** Reagents and conditions: a) MeOH, H<sub>2</sub>SO<sub>4</sub>, 60°C; b) Et<sub>3</sub>N, dioxane, 100°C; c) SnCl<sub>2</sub>•2H<sub>2</sub>O (5 eq) or Zn (5 eq), AcOH-MeOH (1:9), -40°C; d) NH<sub>2</sub>OH•HCl (10 eq)/NaOMe (20 eq)/MeOH, 0°C to rt; e) SnCl<sub>2</sub>•2H<sub>2</sub>O (5 eq), AcOH-MeOH (1:9), 40°C; f) coupling reagent (EDCI), HOBT; g) HOAc, reflux; h) HCO<sub>2</sub>H or CH<sub>3</sub>CO<sub>2</sub>H, reflux; i) NaBH(OAc)<sub>3</sub> or NaBH<sub>3</sub>CN

- Lipophilicity plays an important role for *in vitro* potency for this class of compounds: both HDAC1 enzyme IC<sub>50</sub>s and COLO205 cell IC<sub>50</sub>s have positive correlations with clogP for both A and B (excluding B4) series
- Cellular IC<sub>50</sub>s also have positive correlations with enzyme IC<sub>50</sub>s (Figure 5). Other cell lines such as HCT116, A2780, and PC3 also have correlations with enzymatic potency (data not shown).
- In vitro* activity, metabolic stability, and CYP inhibition were tuned by judicious combination of R<sup>1</sup> and R<sup>2</sup>.
- In general, 2-carbon linker in the basic side chain (R<sup>1</sup> B Series) is more potent than the corresponding 3-carbon-linker (A series) (Entries 1 vs 2 in Table 1).
- Figure 6 reveals this is probably due to a more efficient electrostatic interaction with ASP 99.
- The basic center must be correctly placed (Entries 2 vs 3, 4 vs 5).

Table 1. Effect of R<sup>1</sup> and R<sup>2</sup> on *in vitro* potency

Entry	Compound <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	clogP	HDAC1 IC <sub>50</sub> (μM)	COLO 205 IC <sub>50</sub> (μM)
1	A1b2		<i>n</i> -butyl	4.12	0.150	2.22
2	B1b2 (SB939)		<i>n</i> -butyl	3.61	0.076	0.56
3	b2B1		<i>n</i> -butyl	3.61	0.895	6.52
4	B5b2		<i>n</i> -butyl	2.93	0.090	0.65
5			<i>n</i> -butyl	4.80	3.35	8.10

<sup>a</sup> Compounds are coded by R<sup>1</sup> and R<sup>2</sup> group, e.g., A1b2 means R<sup>1</sup> = A1 (see Figure 3), R<sup>2</sup> = b2 (see Figure 4).

## Results

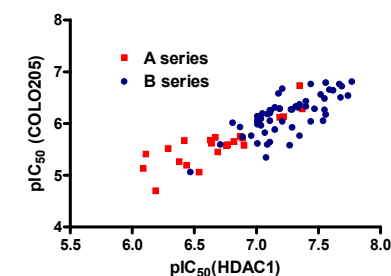


Figure 5. Cellular activity (COLO205) correlates with enzymatic activity (HDAC1).  $pIC_{50} = -\log_{10}IC_{50}$ .

- A number of HLM stable compounds showed significant antitumor activities (Entries 1, 2 and 4 in Table 2).
- Compound B1b2 (SB939) showed better antitumor efficacy than SAHA, LBH589 and PXD101 at MTD or maximum absorbed dose level in this model (Figure 7).
- SB939 also showed broad antitumor activities in other tumor models.<sup>4a</sup>

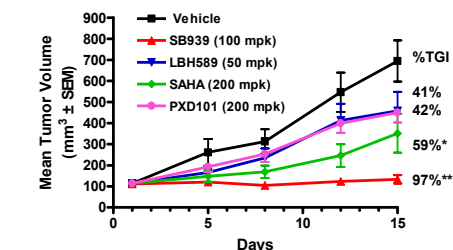


Figure 7. Antitumor activities of SB939, SAHA, LBH589 and PXD101 in HCT116 xenograft model (po, qd x14, n = 7). mpk = mg/kg.

- SB939 has good PK in both mouse and dog (%F 34% and 65%, respectively), and has demonstrated a superior oral PK profile to the agents currently in clinical trials with a higher C<sub>max</sub> and AUC than SAHA, PXD101 and LBH589 at the same dose level.<sup>4b</sup> In addition, SB939 is enriched in tumor tissues.
- Detailed studies on PK-PD correlations showing a strong response at the 3 hour time point can be found in poster #83 (V. Novotny-Diermayr, et al.)

## Conclusions

- SB939 is a potent pan-HDAC inhibitor with excellent drug-like properties (logD<sub>pH 7.4</sub> = 2.1, solubility at pH5 >10 mg/mL), highly effective in *in vivo* tumor models, has high and dose-proportional oral bioavailability and very good ADME, safety and pharmaceutical properties.
- SB939 has a prolonged duration of action and is enriched in tumor tissue which may contribute to its potent anti-tumor activity.
- SB939 is currently being tested in phase I trials in both hematological and solid tumor patients and preliminary data show that the superior preclinical profile is translated to the clinic (see clinical poster #413).

## References

- Wang, H.; et al. 232<sup>nd</sup> ACS National Meeting (2006), Abstract No. Medi #146 and #575.
- Venkatesh, P. R.; et al. *Biol. Pharm. Bull.* **2007**, *30*, 1021.
- Finnin, M. S.; et al. *Nature* **1999**, *401*, 188.
- Sangthongpitag, K.; et al. (2006) 18<sup>th</sup> EORTC-NCI-AACR Symposium, Prague Congress Centre, Prague, Czech Republic, a) Abstract number 162, b) Abstract number 166.

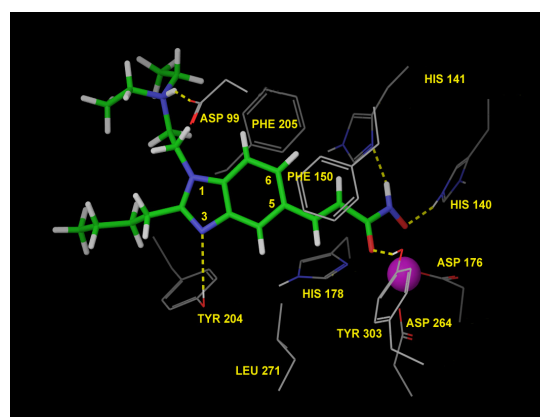


Figure 6. SB939 docked into the HDAC1 homology model (built based on the HDLP X-ray structure 1C3R<sup>3</sup>). Key interactions between the basic centers with Asp 99 and Tyr 204 contribute to the potency.