Pracinostat

Cat. No.: HY-13322

CAS No.: 929016-96-6

Molecular Formula: $C_{20}H_{30}N_4O_2$

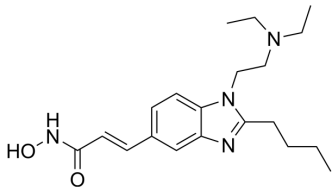
Molecular Weight: 358.48

Target: HDAC; Apoptosis; Beta-lactamase

Pathway: Cell Cycle/DNA Damage; Epigenetics; Apoptosis; Anti-infection

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (697.39 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7896 mL	13.9478 mL	27.8956 mL
	5 mM	0.5579 mL	2.7896 mL	5.5791 mL
	10 mM	0.2790 mL	1.3948 mL	2.7896 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.75 mg/mL (7.67 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (5.80 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.80 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pracinostat is a potent histone deacetylase (HDAC) inhibitor, with IC_{50}s of 40-140 nM, used for cancer research. Pracinostat also inhibits metallo-β-lactamase domain-containing protein 2 (MBLAC2) hydrolase activity with an EC_{50} below 10 nM[1][4].

IC_{50} & Target

HDAC10 40 nM (IC_{50})	HDAC3 43 nM (IC_{50})	HDAC5 47 nM (IC_{50})	HDAC1 49 nM (IC_{50})
HDAC4 56 nM (IC_{50})	HDAC9 70 nM (IC_{50})	HDAC11 93 nM (IC_{50})	HDAC2 96 nM (IC_{50})

	HDAC7 137 nM (IC_{50})	HDAC8 140 nM (IC_{50})	HDAC6 1008 nM (IC_{50})	MBLAC2 <10 nM (EC50)

In Vitro

Pracinostat (SB939) is a potent novel hydroxamate-based inhibitor of HDACs class I, II, and IV, inhibiting the isolated enzymes with a K_i of 19 to 48 nM (class I), 16 to 247 nM (class II), and 43 nM (class IV), but with no activity against the class III isoenzyme SIRT I. SB939 has effects on HCT-116 colon cancer cell line and the HL-60 acute myeloid leukemia cell line, with IC_{50}s of 0.48 μM and 70 nM, respectively. SB939 does not inhibit the proliferation of normal human dermal fibroblasts at concentrations up to 100 μM[1]. Pracinostat (SB939, compound 3) inhibits CYP2C19 with IC_{50} of 5.78 μM. SB939 shows potent activities against A2780, COLO 205, HCT-116, and PC-3 cell lines, with IC_{50}s of 0.48 ± 0.21, 0.56 ± 0.08, 0.48 ± 0.27, and 0.34 ± 0.06[2]. Pracinostat downregulates JAK and FLT3 signaling in $JAK2^{V617F}$ and FLT-ITD cell lines, and shows synergy in combination with pacritinib. Pracinostat and pacritinib show in vitro synergy on STAT signaling and apoptosis. Pracinostat potently inhibits proliferation of different AML subtypes as a single agent and is synergistic with pacritinib in $JAK2^{V617F}$ or FLT3-ITD AML cell lines[3].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Pracinostat (SB939, 25-100 mg/kg) shows significant dose-dependent growth inhibition of HCT-116 xenografts. SB939 selectively accumulates in tumor tissue. SB939 (50 or 75 mg/kg) exhibits anti-tumor activities in the Apcmin genetic colon cancer mouse model[1]. Pracinostat (25 or 50 mg/kg per day for 21 days) induces significant inhibition of tumor growth (TGI), by 59 and 116%, respectively, in mice bearing MV4-11 xenografts. Pracinostat (75 mg/kg, q.o.d) in combination with pacritinib is efficacious and synergistic in vivo in two different models of human AML. Pracinostat and pacritinib have synergistic effects on AML-induced plasma cytokines/growth factors/chemokines[3].

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PROTOCOL

Cell Assay [1]

Cells are seeded in 96-well plates at a predetermined optimal density, in the log growth phase, and rested for 24 h (adherent cells) or 2 h (suspension cells), respectively, before treatment with SB939. All experiments are done in triplicates for 96 h, with 1% solvent, using either the CyQUANT Cell proliferation assay kit for adherent cells or the CellTiter96 Aqueous One solution cell proliferation kit for suspension cells, in a total volume of 100 μL with SB939 concentrations from 100 μM to 1.5 nM in nine serial dilution steps. IC_{50} are determined using the XLfit software[1].

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Animal Administration [1]

Male $Apc^{Min/+}$ mice and female C57BL/6 mice are fed a standard rodent diet. Mice with the confirmed mutation, between 16 and 20.5 wk of age, with a positive scoring in the hemocult assay are recruited to the experiment. During treatment, mice are injected i.p. with 40 mg/kg of 5-FU in a volume of 200 μL per 20 g body weight, once daily, for 5 d of treatment, followed by a 9-d recovery period and an additional 5 d of treatment. Treatment with SB939 per oral at 50 or 75 mg/kg once daily is given continuously for 21 d. At the last day of the treatment, the small intestine, caecum, and colon are removed; fixed by multiple injections of 4% PBS-buffered formaldehyde into the gut lumen; cut into segments; and spread flat on a plastic film in a formaldehyde bath. Tumor load is measured in a dissection microscope. Assessment and analysis of the samples are done blinded[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966.
- Drug Des Devel Ther. 2018 Apr 30;12:1009-1017.
- J Mol Med (Berl). 2019 Aug;97(8):1183-1193.
- SSRN. 2023 Jun 20.

- bioRxiv. 2021 Jan 5.

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REFERENCES

[1]. Lechner S, et al. Target deconvolution of HDAC pharmacopoeia reveals MBLAC2 as common off-target. Nat Chem Biol. 2022 Aug;18(8):812-820.

[2]. Novotny-Diermayr V, et al. SB939, a novel potent and orally active histone deacetylase inhibitor with high tumor exposure and efficacy in mouse models of colorectal cancer. Mol Cancer Ther. 2010 Mar;9(3):642-52.

[3]. Wang H, et al. Discovery of (2E)-3-{2-butyl-1-[2-(diethylamino)ethyl]-1H-benzimidazol-5-yl}-N-hydroxyacrylamide (SB939), an orally active histone deacetylase inhibitor with a superior preclinical profile. J Med Chem. 2011 Jul 14;54(13):4694-720.

[4]. Novotny-Diermayr V, et al. The oral HDAC inhibitor pracinostat (SB939) is efficacious and synergistic with the JAK2 inhibitor pacritinib (SB1518) in preclinical models of AML. Blood Cancer J. 2012 May;2(5):e69.

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