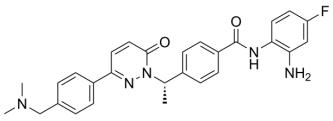
HDAC-IN-56

Cat. No.:	HY-154855
CAS No.:	2814571-89-4
Molecular Formula:	$C_{28}H_{28}FN_5O_2$
Molecular Weight:	485.55
Target:	HDAC
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

HDAC-IN-56 ((S)-17b) is an orally active class I histone deacetylase (HDAC) inhibitor with IC_{50} values of 56.0 ± 6.0, 90.0 ± 5.9, 422.2 ± 105.1, >10000 nM for HDAC1, HDAC2, HDAC3, and HDAC4-11, respectively. HDAC-IN-56 has potent inhibitory activity while strongly increasing intracellular levels of acetylhistone H3 and P21 and effectively inducing G1 cell cycle arrest and apoptosis.HDAC-IN-56 has antitumor activity [1].

IC_{50} & Target

HDAC1	HDAC2	HDAC3
56.0 nM (IC_{50})	90.0 nM (IC_{50})	422.2 nM (IC_{50})

In Vitro

HDAC-IN-56 shows potent and selective inhibition against Class I HDACs 1, 2, and 3, better than that of MS-275 (HY-12163)[1].
HDAC-IN-56 (0.1 μM, 2 h) is metabolized in human, monkey, dog, rat and mouse hepatocytes with significant species differences and was stable in five species of hepatocytes[1].
HDAC-IN-56 (0.01-1 μM, 72 h) effectively induces G1 cell cycle arrest and apoptosis[1].
HDAC-IN-56 (0.01-1 μM, 72 h) treatment increases the intracellular level of acetyl-histone H3 and p21 simultaneously better than that of Tucidinostat (HY-109015) or MS-275 (HY-12163), which implied its strong class I histone deacetylase inhibition[1].
HDAC-IN-56 has an IC_{50} of 139.0 ± 8.0 nM for SKM-1[1].
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HDAC-IN-56 (compuond (S)-17b) Metabolic Stability in Hepatocytes of Five Species (mass spectrum peak area)[1]

HDAC-IN-56 (compuond (S)-17b) [illegible] ([illegible])[1]

no.	human	monkey	dog	rat	mouse
(S)-17b-120 min	132390 (299)	118399 (300)	133963 (347)	133098 (347)	143377 (349)
(S)-17b-0 h	129174 (293)	107142 (267)	150514 (395)	136550 (350)	156075 (392)

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

Cell Cycle Analysis[1]

Cell Line:	SKM-1
Concentration:	0.01, 0.1, 1 μM
Incubation Time:	72 h
Result:	Downregulated the expression of c-Myc and CDK4 at 0.1 μM, which is better than MS-275 (HY-12163) or Tucidinostat (HY-109015).

Apoptosis Analysis[1]

Cell Line:	SKM-1
Concentration:	0.01, 0.1, 1 μM
Incubation Time:	72 h
Result:	Triggered strong apoptosis as determined by Annexin V/PI staining, stronger than MS-275 (HY-12163) or Tucidinostat (HY-109015).

Western Blot Analysis[1]

Cell Line:	SKM-1
Concentration:	0.01, 0.1, 1 μM
Incubation Time:	72 h
Result:	Increased the intracellular level of acetyl-histone H3 and p21 simultaneously better than that of Tucidinostat (HY-109015) or MS-275 (HY-12163).

In Vivo

HDAC-IN-56 (10-80 mg/kg/d, p.o., one month) cause no significant change of body weight, even at high dose of 80 mg/kg per day, the mice can tolerate with the descended body weight compared with the control[1].

HDAC-IN-56 (SD: 10, 20 mg/kg ; ICR: 20, 40 mg/kg, p.o.) represent a favorable pharmacokinetic profile with an oral bioavailability of 47.7% in ICR mice and 39.5% in SD rat, respectively[1].

HDAC-IN-56 (20-60 mg/kg, p.o.) inhibit the tumor growth of MC38 cells in nude mice as expected, when inoculate in immunocompetent C57BL/6 mice show more significant tumor growth inhibition at the same doses, which implie that the immune system may be engaged and somehow activated gain stronger antitumor effect[1].

In vivo pharmacokinetics of HDAC-IN-56 (compuond (S)-17b) in ICR mice and SD rat[1]

HDAC-IN-56□compuond (S)-17b□□ICR□□□SD□□□□□□□□□□□□□[1]

	ICR mice							SD rat						
(S)-17b	dose (mg/kg)	CL (mL/min/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)	AUC_{0-t} (h x ng/mL)	C_{max} (ng/mL)	T_{max} (h)	F (%)	dose (mg/kg)	CL (mL/min/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)	AUC_{0-t} (h x ng/mL)	C_{max} (ng/mL)	T_{max} (h)	F (%)
iv	20	64.4 ± 10.3	5.3 ± 1.2	3.6 ± 0.3	5269 ± 924				10	34.3 ± 8.6	4.1 ± 0.8	1.5 ± 0.2	4935 ± 1068			

po	40	2.5 ± 0.3	5031 ± 441	1963 ± 335	0.83 ± 0.29	47.7	20	2.3 ± 0.6	3895 ± 141	1086 ± 16	2.0039.5		

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

Animal Model:	Male SD rats or ICR mice[1]
Dosage:	10, 20 mg/kg ; ICR: 20, 40 mg/kg
Administration:	Male SD rats or ICR mice (n = 6) were fasted for 12 h before administration and remained fasting for 2 h. SD rats were received 10 and 20 mg/kg via intravenously injection (iv) and oral administration (po), respectively, and ICR mice were received 20 and 40 mg/kg via intravenously injection (iv) and oral administration (po), respectively.
Result:	Epresented a favorable pharmacokinetic profile with an oral bioavailability of 47.7% in ICR mice and 39.5% in SD rat, respectively

Animal Model:	SKM-1 or MC-38 cells xenograft model[1]
Dosage:	20, 40, 60 mg/kg
Administration:	Oral gavage (p.o.).
Result:	Inhibited the tumor growth of MC38 cells in nude mice. Showed more significant tumor growth inhibition at the same doses, which implie that the immune system may be engaged and somehow activated HDAC-IN-56 to gain stronger antitumor effect.

REFERENCES

[1]. Li D, et al. Discovery of (S)-N-(2-Amino-4-fluorophenyl)-4-(1-(3-(4-((dimethylamino)methyl)phenyl)-6-oxopyridazin-1(6H)-yl)ethyl) benzamide as Potent Class I Selective HDAC Inhibitor for Oral Anticancer Drug Candidate. J Med Chem. 2023 May 25;66(10):7016-7037.

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