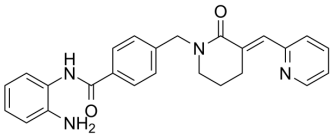
HDAC-IN-31

Cat. No.:	HY-144293
CAS No.:	1916505-13-9
Molecular Formula:	$C_{25}H_{24}N_4O_2$
Molecular Weight:	412.48
Target:	Apoptosis; HDAC
Pathway:	Apoptosis; Cell Cycle/DNA Damage; Epigenetics
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

HDAC-IN-31 is a potent, selective and orally active HDAC inhibitor with IC_{50}s of 84.90, 168.0, 442.7, >10000 nM for HDAC1, HDAC2, HDAC3, HDAC8, respectively. HDAC-IN-31 induces apoptosis and cell cycle arrests at G2/M phase. HDAC-IN-31 shows good antitumor efficacy. HDAC-IN-31 has the potential for the research of diffuse large B-cell lymphoma[1].

IC_{50} & Target

HDAC1	HDAC2	HDAC3	HDAC8
84.90 nM (IC_{50})	168.0 nM (IC_{50})	442.7 nM (IC_{50})	>10000 nM (IC_{50})

In Vitro

HDAC-IN-31 (compound 24g) (2 μM) shows growth-inhibitory activities with the inhibition rate of 2.32%, 44.01%, 48.53%, 64.94% for TMD-8, HCT 116, A549, MDA-MB-231 cells[1].

HDAC-IN-31 (1 μM) shows selectivity with the IC_{50}s of 84.9, 168.0, 442.7, >10000 nM for HDAC 1, HDAC 2, HDAC 3, HDAC 8, and 81.20%, 84.43%, 88.07%, 92.34%, 96.88%, 91.98% enzyme activity for HDAC4, HDAC 5,HDAC 7, HDAC9, HDAC 6, HDAC 11, respectively[1].

HDAC-IN-31 (2.5, 5, 7.5, 10 μM; 24 h) increases the expression of HDAC1, Ace-H3, Ace-H4, Cleaved PARP, Cleaved Caspase-3 in a dose-dependent manner[1].

HDAC-IN-31 (0-4 μM; 24 h)induce apoptosis and cell cycle arrests in G2/M phase in a dose-dependent manner[1].

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

Cell Proliferation Assay[1]

Cell Line:	MDA-MB-231, A549, NCI-H460, HCT-116,SK-OV-3, HT-29, COLO 678, NCI-H441, 22Rv1, 786-O, TMD-8, DOHH-2, CCRF-CEM, SU-DHL-2, REC-1, MOLT-4, HUT-78, RS4;11 cells
Concentration:	0-20 μM
Incubation Time:	72 h
Result:	Showed a broad spectrum of antitumor activity with the IC_{50}s of 2.29, 2.85, 1.58, 1.16, 3.17, 2.41, 8.02, 2.62, 1.14, 0.60, 0.31, 0.39, 0.48, 0.51, 0.33, 0.38, 0.80, 0.47 μM for MDA-MB-231, A549, NCI-H460, HCT-116, SK-OV-3, HT-29, COLO 678, NCI-H441, 22Rv1, 786-O, TMD-8, DOHH-2, CCRF-CEM, SU-DHL-2, REC-1, MOLT-4, HUT-78, RS4;11 cells, respectively.

Western Blot Analysis[1]

Cell Line:	TMD-8 cells

Concentration:	2.5, 5, 7.5, 10 μM
Incubation Time:	24 h
Result:	Promoted the HDAC1, HDAC2, HDAC3 substrate Ace-H3 and Ace-H4 acetylation with a dose-dependent manner.

Apoptosis Analysis[1]

Cell Line:	TMD-8 cells
Concentration:	0.5, 1, 2, 4 μM
Incubation Time:	24 h
Result:	Induced cell apoptosis at a concentration-dependent manner.

Cell Cycle Analysis[1]

Cell Line:	TMD-8 cells
Concentration:	250, 500, 1000 nM
Incubation Time:	24 h
Result:	Arrested the cell cycle at G2/M phase in a dose-dependent manner.

In Vivo

HDAC-IN-31 (2 mg/kg for i.v.; 10, 100 mg/kg for p.o.) shows good bioavailability with a significant dose dependent manner[1].
HDAC-IN-31 (50, 100 mg/kg; p.o, daily for 21 consecutive days) shows good antitumor efficacy in a TMD-8 xenograft model without obvious toxicity[1].
Pharmacokinetic Parameters of HDAC-IN-31 in mice[1].

Parameters	Unit	24 g (25 mg/kg)
C_{max}	$ng{\cdot}h{\cdot}mL^{-1}$	3100±231
$T_{1/2(po)}$	h	4.4±0.3
$AUC_{0\text{-}inf(iv)}$	$ng{\cdot}h{\cdot}mL^{-1}$	1040±142
$AUC_{0\text{-}inf(po)}$	$ng{\cdot}h{\cdot}mL^{-1}$	5180±252
MRT_{PO}	h	2.6±0.4
F	%	39.9±2.1

ICR mouse; 2 mg/kg for i.v.; 25 mg/kg for p.o.[1].
Pharmacokinetic Parameters of HDAC-IN-31 in tumor models[1].

Parameters	Unit	po (25 mg/kg)	po (50 mg/kg)	po (100 mg/kg)
C_{max}	$ng{\cdot}h{\cdot}mL^{-1}$	1700±317	14700±1024	10700±1001

AUC_{0-t}	$ng{\cdot}h{\cdot}mL^{-1}$	1220±242	9710±314	9740±230
AUC_{0-inf}	$ng{\cdot}h{\cdot}mL^{-1}$	1230±165	9730±341	9770±332
MRT_{0-t}	h	0.750±0.043	0.812±0.023	1.43±0.56
MRT_{0-inf}	h	0.805±0.086	0.821±0.041	1.51±0.32

Mouse; 25, 50, 100 mg/kg for p.o.[1].
Pharmacokinetic Parameters of HDAC-IN-31 in tumor models[1].

PK parameters	Unit	iv (2 mg/kg)	po (10 mg/kg)	po (100 mg/kg)
C_{max}	$ng{\cdot}h{\cdot}mL^{-1}$		3960±413	58300±1352
$T_{1/2}$	h	0.427±0.016	1.31±0.27	1.63±0.52
AUC_{0-inf}	$ng{\cdot}h{\cdot}mL^{-1}$	1250±132	2670±286	57200±1047
MRT	h	0.402±0.032	0.919±0.052	0.897±0.041
CL	$mL{\cdot}kg{\cdot}min^{-1}$	27.2±1.2		
F	%		45.6±1.2	91.8±2.3

ICR mice; 2 mg/kg for i.v.; 10, 100 mg/kg for p.o.[1].
Pharmacokinetic Parameters of HDAC-IN-31 in tumor models[1].

PK parameters	Unit	Monkey		Dog	
		iv (1 mg/kg)	po (10 mg/kg)	iv (1 mg/kg)	po (10 mg/kg)
C_{max}	$ng{\cdot}h{\cdot}mL^{-1}$		8520±301		4740±243
$T_{1/2}$	h	4.31±0.56	9.14±0.32	1.65±0.41	1.51±0.33
AUC_{0-inf}	$ng{\cdot}h{\cdot}mL^{-1}$	15700±1842	53200±1241	2550±365	15100±2004
MRT	h	3.41±0.12	8.28±0.32	2.26±0.41	2.71±0.32
CL	$mL{\cdot}kg{\cdot}min^{-1}$	1.35±0.21		6.72±0.35	
Vd_{ss}	$L{\cdot}kg^{-1}$	0.34±0.22		0.55±0.04	
F	%		27.6±2.1		58.9±1.2

Dogs and monkeys; 1 mg/kg for i.v., 10 mg/kg for p.o. for monkey; 1 mg/kg for i.v., 10 mg/kg for p.o. for dog[1].

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

Animal Model:	ICR mice[1]
Dosage:	2 mg/kg for i.v.; 25 mg/kg for p.o.(DMSO/PEG200/saline = 20:20:60, v/v/v)
Administration:	I.v. or p.o.
Result:	Showed high oral bioavailability (F=40%).

Animal Model:	Mouse[1]
Dosage:	25, 50, 100 mg/kg
Administration:	P.o.
Result:	Did not exhibit a significant dose dependent for oral administration.

Animal Model:	ICR mice[1]
Dosage:	2, 10, 100 mg/kg (into the form of hydrochloride)
Administration:	2 mg/kg for i.v.; 10, 100 mg/kg for p.o.
Result:	Showed good bioavailability with a significant dose dependent.

Animal Model:	Dogs and monkeys[1]
Dosage:	1, 10 mg/kg
Administration:	1 mg/kg for i.v.; 10 mg/kg for p.o.
Result:	Showed good pharmacokinetic characteristics for different species.

Animal Model:	5-6 weeks, female CB.17 SCID mice (TMD-8 tumor xenografts)[1]
Dosage:	50, 100 mg/kg
Administration:	P.o, daily for 21 consecutive days
Result:	Inhibited the tumor growth with the inhibition rate of 77% and had no significant effect on the internal organs of mice at 100 mg/kg/d.

REFERENCES

[1]. Cui H,et al. Design and synthesis of HDAC inhibitors to enhance the therapeutic effect of diffuse large B-cell lymphoma by improving metabolic stability and pharmacokinetic characteristics. Eur J Med Chem. 2022 Feb 5;229:114049.

Caution: Product has not been fully validated for medical applications. For research use only.

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