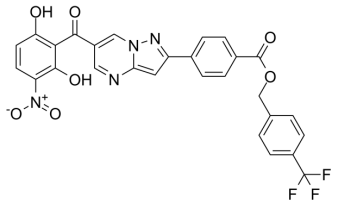
DDO-2728

Cat. No.:	HY-155489
CAS No.:	3029515-97-4
Molecular Formula:	$C_{28}H_{17}F_3N_4O_7$
Molecular Weight:	578.45
Target:	Anaplastic lymphoma kinase (ALK); Apoptosis
Pathway:	Protein Tyrosine Kinase/RTK; Apoptosis
Storage:	Powder -20°C 3 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (216.09 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7288 mL	8.6438 mL	17.2876 mL
	5 mM	0.3458 mL	1.7288 mL	3.4575 mL
	10 mM	0.1729 mL	0.8644 mL	1.7288 mL

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

BIOLOGICAL ACTIVITY

Description

DDO-2728 (compound 19) is a selective AlkB homologue 5 (ALKBH5) inhibitor with an IC_{50} of 2.97 μM. DDO-2728 increases the abundance of N^6 methyladenosine (m^6A) modifications, inducing cell apoptosis and cycle arrest. DDO-2728 suppresses tumor growth in the MV4−11 xenograft model with favorable safety profile, shows the potential of targeting ALKBH5 in cancer research[1].

IC_{50} & Target

AlkB homologue 5 (ALKBH5) IC_{50}: 2.97 μM[1]

In Vitro

DDO-2728 (0-40 μM, 48 h) increases m^6A methylation levels in the MOLM-13, HEK293and MV4−11 cells over a concentration gradient[1].

DDO-2728 (0.01-100 μM, 72 h) inhibits the proliferation of MOLM-13 and MV4−11 cells with IC_{50}s of 0.45 and 1.2 μM respectively, and showes a relatively weak toxicity in HEK293 and HUVECs[1].

DDO-2728 (20 μM, 48 h) significantly arrests the cell cycle of MOLM-13 and MV4−11 cells at the G1/M phase[1].

DDO-2728 (5, 10 μM, 48 h) concentration-dependently induces cell apoptosis of MV4−11 and MOLM-13 cells[1].

DDO-2728 (20 μM, 24 h) decreases the half-lives of TACC3 mRNA in MOLM-13 and MV4−11 cells[1].

DDO-2728 (0-10 μM, 48 h) significantly reduces the abundance of TACC3 and c-Myc in MOLM-13 and MV4−11 cells at both mRNA and protein levels[1].

Metabolic Stability in Rat and Human Plasma and Liver Microsomes[1]

Species	Plasma $T_{1/2}$ (min)	Microsome $T_{1/2}$ (min)	Microsome CL (μL/min/mg)
Human	624	430	3.2
Rat	251	13.8	100.4

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

Cell Proliferation Assay[1]

Cell Line:	MOLM-13, MV4-11, HEK293, HUVEC
Concentration:	0.01-100 μM
Incubation Time:	72 h
Result:	Inhibited the proliferation of MOLM-13 and MV4−11 cells with IC_{50}s of 0.45 and 1.2 μM respectively, didn't show visual cytotoxicity in HEK293 and HUVECs under 1 μM.

Apoptosis Analysis[1]

Cell Line:	MOLM-13, MV4-11
Concentration:	0, 5, 10 μM
Incubation Time:	48 h
Result:	Induced cell apoptosis of MV4−11 and MOLM-13 cells concentration-dependently, apoptosis rate for MV4−11 increased from 7.17% to 55.4%, apoptosis rate for MOLM-13 increased from 6.49% to 31.5%.

Cell Cycle Analysis[1]

Cell Line:	MOLM-13, MV4-11
Concentration:	20 μM
Incubation Time:	48 h
Result:	Arrested the cell cycle of MOLM-13 and MV4−11 cells at the G1/M phase as no G2/M phase cells exist.

In Vivo

DDO-2728 (10-40 mg/kg, i.p., daily for 14 d) effectively inhibits tumor growth in MV4−11 xenograft nude mice.[1].

Pharmacokinetic Parameters of DDO-2728 in Rats[1]

Parameter	Rat (i.v., 2mg/kg)	Rat (i.p., 10mg/kg)
$T_{1/2}$ (min)	36.7 ± 3.2	148.3 ± 4.6
C_{max} (ng/mL)	13388.3 ± 784.5	2337.5 ± 295.7

T_{max} (min)		30
$AUC_{0-\infty}$ (min·μg/mL)	404.3 ± 58.6	349.1 ± 26.1
Vz_F_obs (mL/kg)	263.6 ± 17.5	6177.6 ± 650.2
Cl_F_obs (mL/min/kg)	5.0 ± 0.5	28.8 ± 2.2
MRT (min)	77.8 ± 15.5	168.2 ± 1.2
F (%)		17.3

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

Animal Model:	MV4−11 xenograft nude mice [1]
Dosage:	10, 20, and 40 mg/kg
Administration:	Intraperitoneal injection (i.p.) daily for 14 d
Result:	Inhibited tumor growth significantly even at a concentration of 10 mg/kg. No significant change in the weight of the mice and the main organs during the treatment, the organ weight of test group mice was the same as vehicle group, no obvious injury damage was observed in the HE staining images of organ tissues.

REFERENCES

[1]. Zheng-Yu Jiang, et al. Discovery of Pyrazolo[1,5-a]pyrimidine Derivative as a Novel and Selective ALKBH5 Inhibitor for the Treatment of AML. Journal of Medicinal Chemistry. 2023 Article ASAP.

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