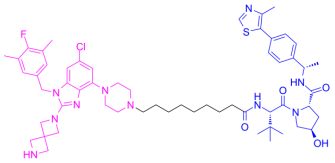
PROTAC SOS1 degrader-1

Cat. No.:	HY-145737
CAS No.:	2913185-35-8
Molecular Formula:	$C_{57}H_{76}ClFN_{10}O_4S$
Molecular Weight:	1051.79
Target:	PROTACs; Ras
Pathway:	PROTAC; GPCR/G Protein; MAPK/ERK Pathway
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	PROTAC SOS1 degrader-1 is a potent PROTAC SOS1 degrader with an DC_{50} of 98.4 nM. PROTAC SOS1 degrader-1 shows antiproliferation activity in cancer cells with various KRAS mutations. PROTAC SOS1 degrader-1 shows antitumor effect with low toxicity[1].
IC_{50} & Target	DC_{50}: 98.4 nM (SOS1)[1]

In Vitro

PROTAC SOS1 degrader-1 (compound 9d) (0.1, 1 μM) shows SOSI degradation activity with an SOS1 protein degradation of 56.2 and 92.5% at 0.1 and 1 μM, respectively[1].

PROTAC SOS1 degrader-1 (0-2000 nM; 24 h) exhibits SOS1 degradation activity with an DC_{50} of 98.4 nM in a dose- and time-dependent manner in NCI-H358 cells[1].

PROTAC SOS1 degrader-1 (0-2500 nM; 24 h) dose-dependently reduced the SOS1 protein level but showed no effect on SOS2 and KRAS up to 2.5 μM in NCI-H358 and AsPc-1 cells[1].

PROTAC SOS1 degrader-1 (0-2000 nM; 24 h) reduces the expression of KRAS-GTP, induced ERK phosphorylation with an IC_{50} value of 72.3 nM, and significantly increases the pERK level after 6-24 h[1].

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

Western Blot Analysis[1]

Cell Line:	NCI-H358 cells
Concentration:	0-2000 nM
Incubation Time:	0-24 h
Result:	Decreased the expression of SOS1 in a dose- and time-dependent manner in NCI-H358 cells.

RT-PCR[1]

Cell Line:	NCI-H358 cells
Concentration:	1 μM
Incubation Time:	24, 48, 72 h
Result:	Showed no effffect on SOS2 mRNA expression.

Cell Proliferation Assay[1]

Cell Line:	NCI-H358, MIA-PaCa2, AsPC-1, SK-LU-1, SW620, A549 cells
Concentration:	0-10000 nM
Incubation Time:	7 days
Result:	Showed anti-proliferation activity with an IC_{50}s of 0.525, 0.218, 0.307, 0.115, 0.199, 0.232 μM and DC_{50}s of 0.098, 0.255, 0.119, 0.104, 0.125, 0.022 μM for NCI-H358, MIA-PaCa2, AsPC-1, SK-LU-1, SW620, A549 cells, respectively.

In Vivo

PROTAC SOS1 degrader-1 (10 mg/kg; i.p.) shows good PK profile with low toxicity[1].

PROTAC SOS1 degrader-1 (0, 10, 20 mg/kg; i.p.; once a day for 3 weeks) shows significant anti-tumor activities in the xenograft mouse model[1].

Pharmacokinetic Parameters of PROTAC SOS1 degrader-1 in BALB/c mice[1].

compound	dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{INF} (h*ng/mL)	$MRT_{INF\text{-}obs}$(h)
9d	10	8.64±0.31	0.250v±0	1221±132	3895±335	4420±363	10.2±0.4

Male BALB/c mice; 10 mg/kg for i.p.[1].

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Animal Model:	Male BALB/c mice[1]
Dosage:	10 mg/kg (dissolved in solution containing dimethyl sulfoxide, PEG400, and 10%hydroxypropyl-β-cyclodextrin in water (5/5/90, v/v/v))
Administration:	I.p.
Result:	Showed good PK profile with high exposure ($AUC_{0-\infty}$ = 4420 h*ng/mL) andmaximum concentration (C_{max} = 1221 ng/mL) in mouse plasma.

Animal Model:	6-8 weeks, BALB/c mice [1]
Dosage:	0, 10, 20 mg/kg
Administration:	I.p.; once a day for a week
Result:	Showed low toxicity for mouse.

Animal Model:	6-8 weeks, BALB/c nude mice (NCI-H358 tumor xenografts) [1]
Dosage:	0, 10, 20 mg/kg
Administration:	I.p.; once a day for 3 weeks;
Result:	Inhibited the tumor growth by 72.5 and 86.1% at 10 and 20 mg/kg, respectively.

Animal Model:	6-8 weeks, BALB/c nude mice (NCI-H358 tumor xenografts)[1]

Dosage:	0, 20, 50 mg/kg
Administration:	Intratumoral injection; twice-weekly for 5 weeks
Result:	Significantly prevented tumor growth in vivo with a good safety profile.

REFERENCES

[1]. Zhou C, et al. Discovery of the First-in-Class Agonist-Based SOS1 PROTACs Effective in Human Cancer Cells Harboring Various KRAS Mutations. J Med Chem. 2022 Mar 10;65(5):3923-3942.

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

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