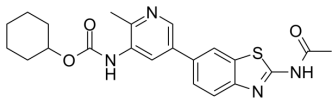
PK68

Cat. No.:	HY-128348
CAS No.:	2173556-69-7
Molecular Formula:	$C_{22}H_{24}N_4O_3S$
Molecular Weight:	424.52
Target:	RIP kinase
Pathway:	Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 30 mg/mL (70.67 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3556 mL	11.7780 mL	23.5560 mL
5 mM	0.4711 mL	2.3556 mL	4.7112 mL
10 mM	0.2356 mL	1.1778 mL	2.3556 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: ≥ 3 mg/mL (7.07 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.90 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.90 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PK68 is a potent orally active and specifical type II inhibitor of receptor-interacting kinase 1 (RIPK1) with an IC_{50} of ~90 nM, displays inhibition of RIPK1-dependent necroptosis. PK68 powerfully ameliorates TNF-induced systemic inflammatory response syndrome, and can be used for the research of inflammatory disorders and cancer metastasis[1].

IC_{50} & Target

RIPK1 90 nM (IC_{50})	RIPK1 23 nM (EC50)

In Vitro

PK68 has highly potent inhibition of TNF-induced necroptosis with EC_{50} values of 23 nM and 13 nM in human and mouse cells, respectively[1].
PK68 is a highly selective inhibitor of RIPK1 kinase activity with IC_{50} value of 90 nM[1].
PK68 (100 nM, 1 h) blocks necroptosis through the suppression of RIPK3 function or signaling upstream of RIPK3 activation[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	Bone marrow-derived macrophages, NIH3T3-RIPK3 cells
Concentration:	100 nM
Incubation Time:	1 h
Result:	PK68 block cellular activation of RIPK1, RIPK3, and MLKL upon necroptotic stimuli. PK68 inhibit TNF-induced necroptosis but not RIPK3 dimerization-induced cell death in NIH3T3-RIPK3 cells.

Western Blot Analysis[1]

Cell Line:	HT-29 cells
Concentration:	100 nM
Incubation Time:	1 h
Result:	Completely abolished phosphorylation of RIPK1, RIPK3, and MLKL.

Immunofluorescence[1]

Cell Line:	HT-29 cells
Concentration:	100 nM
Incubation Time:	1 h
Result:	Prevented generation of RIPK3 puncta.

In Vivo

PK68 (5 mg/kg, 25 mg/kg; oral gavage; daily; for 7 days) or (2 mg/kg, i.v.; 10 mg/kg, p.o.; for 14 days) exhibits a favorable pharmacokinetic profile and no obvious toxicity in mice[1].
PK68 (1 mg/kg, i.p.) ameliorates TNF-induced systemic inflammatory response syndrome[1].
PK68 (5 mg/kg, i.v.) inhibits RIPK1 that results in attenuated tumor cell transmigration across the endothelial barrier and preventive suppression of tumor metastasis[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	C57BL/6 mice[1]
Dosage:	5 mg/kg, 25 mg/kg
Administration:	5 mg/kg, 25 mg/kg; oral gavage; daily; for 7 days
Result:	Exhibited favorable pharmacokinetic profiles and no obvious toxicity in mice treated with a 14-day course at a dose of 25 mg/kg.

Animal Model:	C57BL/6 mice[1]

Dosage:	2 mg/kg, 10 mg/kg
Administration:	2 mg/kg, i.v.; 10 mg/kg, p.o; for 14 days
Result:	

	PO (Gavage)	IV (Bolus)
T_{max} (hr)	0.5	
C_{max} (ng/mL)	2423	
AUC_{0-24} (ng/mL•hr)	4821	1588
AUCINF (ng/mL•hr)	4897	1590
$t_{1/2}$ (hr)	1.3	1.0
MRT (hr)	1.8	0.8
CL (mL/hr/kg)		1258
CL (mL/min/kg)		21
Vss (mL/kg)		1009
Vss (L/kg)		1.0
F(%)	61	

Animal Model:	C57BL/6 mice[1]
Dosage:	1 mg/kg
Administration:	1 mg/kg, i.p.
Result:	Provided effective protection against TNFα-induced lethal shock.

Animal Model:	C57BL/6 mice[1]
Dosage:	5 mg/kg
Administration:	5 mg/kg, i.v.
Result:	Significantly reduced the number of pulmonary metastasis nodules, decreased lung metastasis, decreased number of RFP-LL/2 cells, attenuated transmigration of RFP-LL/2 cells through the endothelial cell monolayer and had no obvious influence on the proliferation rate and invasion ability of B16-F10 or RFP-LL/2 cells without the endothelial cell monolayer in vitro.

REFERENCES

[1]. Jue Hou, et al. Discovery of potent necroptosis inhibitors targeting RIPK1 kinase activity for the treatment of inflammatory disorder and cancer metastasis. Cell Death Dis. 2019 Jun 24;10(7):493.

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