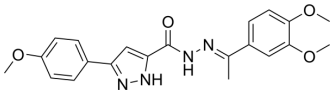
SKI-178

Cat. No.:	HY-12892
CAS No.:	1259484-97-3
Molecular Formula:	$C_{21}H_{22}N_4O_4$
Molecular Weight:	394.42
Target:	SphK; Apoptosis
Pathway:	Immunology/Inflammation; Apoptosis
Storage:	Powder -20°C 3 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (126.77 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5354 mL	12.6768 mL	25.3537 mL
	5 mM	0.5071 mL	2.5354 mL	5.0707 mL
	10 mM	0.2535 mL	1.2677 mL	2.5354 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (6.34 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.34 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

SKI-178 is a potent sphingosine kinase-1 (SphK1) and SphK2 inhibitor. SKI-178 is cytotoxic at IC_{50} concentrations ranging from 1.8 to 0.1 μM in both agent sensitive and multi-agent resistant cancer cell lines (i.e., MTR3, NCI-ADR and HL60/VCR cells). SKI-178 induces apoptosis in a CDK1-dependent manner in human acute myeloid leukemia cell lines[1][2].

IC_{50} & Target	SphK1	SphK2

In Vitro

SKI-178 (5 μM; 24 hours)-induced apoptotic cell death correlates with prolonged Bcl-2 phosphorylation[1].

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

Apoptosis Analysis[1]

Cell Line:	HL-60 cells
Concentration:	5 μM
Incubation Time:	24 hours
Result:	JNK activity (indicated by phosphorylation at Thr183/Tyr185) increased in a time-dependent manner starting as early as 2 hours continued to increase for at least 24 hours. There was a concomitant increase in apoptotic cell death indicated by the cleavage of caspase-7. Bcl-2 phosphorylation at Ser70 increased with time in response to SKI-178 treatment, reaching maximal levels at 8 hours, which was consistent with the timing of caspase-7 activation.

In Vivo

SKI-178 (20 mg/kg; retro-orbital injection under isoflurane anesthesia) inhibits leukemic progression in the MLL-AF9 model[3].

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Animal Model:	MLL-AF9 mouse model (leukemic mice)[3]
Dosage:	20 mg/kg
Administration:	Retro-orbital injection under isoflurane anesthesia; three times per week for 1 and 3 weeks
Result:	White blood cell (WBC) counts decreased from their initial 104 cells/μL levels and continued to decline after 3 weeks of treatment until they reached normal levels (~4×103 cells/μL).

REFERENCES

[1]. Hengst JA, et al. SKI-178: A Multitargeted Inhibitor of Sphingosine Kinase and Microtubule Dynamics Demonstrating Therapeutic Efficacy in Acute Myeloid Leukemia Models. Cancer Transl Med. 2017;3(4):109-121.

[2]. Hengst JA, et al. Development of a sphingosine kinase 1 specific small-molecule inhibitor. Bioorg Med Chem Lett. 2010;20(24):7498-7502.

[3]. Dick TE, et al. The apoptotic mechanism of action of the sphingosine kinase 1 selective inhibitor SKI-178 in human acute myeloid leukemia cell lines. J Pharmacol Exp Ther. 2015;352(3):494-508.

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