R-268712

Cat. No.: HY-12953

CAS No.: 879487-87-3

Molecular Formula: $C_{20}H_{18}FN_5O$

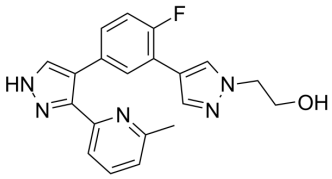
Molecular Weight: 363.39

Target: TGF-β Receptor; TGF-beta/Smad; Anaplastic lymphoma kinase (ALK)

Pathway: TGF-beta/Smad; Stem Cell/Wnt; Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (343.98 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7519 mL	13.7593 mL	27.5186 mL
	5 mM	0.5504 mL	2.7519 mL	5.5037 mL
	10 mM	0.2752 mL	1.3759 mL	2.7519 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: ≥ 2.08 mg/mL (5.72 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.72 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.72 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

R-268712 is an orally active and selective ALK-5 inhibitor, with an IC_{50} of 2.5 nM. R-268712 inhibits the phosphorylation of Smad3 in a dose-dependent manner with an IC_{50} of 10.4 nM. R-268712 suppresses glomerulonephritis as well as glomerulosclerosis by inhibiting TGF-β signaling, which can be used in studies of renal fibrosis and cancer[1][2].

IC_{50} & Target

TGFBR1	Smad3
2.5 nM (IC_{50})	10.4 nM (IC_{50})

In Vitro

R-268712 (3, 10, 30, 100, 300 nM; 1 h) inhibits the phosphorylation of Smad3 in a dose-dependent manner with an IC_{50} of 10.4 nM in HFL-1 cells[1].R-268712 (3, 10, 30, 100, 300 nM; 72 h) inhibits myofibroblast transdifferentiation (MTD) from fibroblasts in a dose-dependent manner without inhibition of cell growth in HFL-1cells[1].

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

Cell Viability Assay[1]

Cell Line:	HFL-1 cells
Concentration:	3, 10, 30, 100, 300 nM
Incubation Time:	1 or 72 h
Result:	Inhibited the phosphorylation of Smad3 in a dose-dependent manner with an IC_{50} of 10.4 nM when incubation 1 h. Suppressed myofibroblast transdifferentiation (MTD) from fibroblasts in a dose-dependent manner without inhibition of cell growth when incubation after 72 h.

In Vivo

R-268712 (0.3, 1, 3, 10 mg/kg; p.o.; single) shows AUC_{0-24} values of 0.075, 0.28, 1.6 and 8.2 μg•h/mL for dosages of 0.3, 1, 3, 10 mg/kg, respectively[2].

R-268712 (1, 3, 10 mg/kg; p.o.; single daily for 3 days) inhibits renal luciferase activity in a dose-dependent manner in UUO model[2].

R-268712 (0.3, 1 mg/kg; p.o.; single daily for 33 days) shows renoprotective effects (improves and maintains renal function as well as inhibits glomerular sclerosis) on Thy1 nephritis model when at dosage of 1 mg/kg[2].

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

Animal Model:	Male WKY/Hos rats[2].
Dosage:	0.3, 1, 3, and 10 mg/kg
Administration:	Oral administration; single.
Result:	Pharmacokinetic Parameters of R-268712 in male WKY/Hos rats (n=4)[2].

	PO (0.3 mg/kg)	PO (1 mg/kg)	PO (3 mg/kg)	PO (10 mg/kg)
AUC_{0-24} (μg•h/mL)	0.075	0.28	1.6	8.2

Animal Model:	Male Col1a1-Luc Tg rats (10 to14-week-old; UUO model; n=5-6)[2].
Dosage:	1, 3, 10 mg/kg
Administration:	Oral administration; single daily for 3 days.
Result:	Suppressed activity of renal luciferase in a dose-dependent manner.

Animal Model:	Male WKY/Hos rats (4-week-old; Thy1 nephritis model; n=7)[2].
Dosage:	0.3, 1 mg/kg
Administration:	Oral administration; single daily for 33 days.

Result:	Significantly reduced proteinuria at day 21(the repression continued until day 28), and serum creatinine level (dosage at 1 mg/kg). Apparently suppressed glomerular sclerosis by 28% and reduced the increase of the hydroxyproline content when at 1 mg/kg. Suppressed the activation of mesangial parenchymal cell and the injury of podocyte on the basis of TGF-β signaling inhibition at 1 mg/kg.

REFERENCES

[1]. Terashima H, et al. Attenuation of pulmonary fibrosis in type I collagen-targeted reporter mice with ALK-5 inhibitors. Pulm Pharmacol Ther. 2019 Feb;54:31-38.

[2]. Terashima H, et al. R-268712, an orally active transforming growth factor-β type I receptor inhibitor, prevents glomerular sclerosis in a Thy1 nephritis model. Eur J Pharmacol. 2014 Jul 5;734:60-6.

[3]. Wang H, et al. Development of small molecule inhibitors targeting TGF-β ligand and receptor: Structures, mechanism, preclinical studies and clinical usage. Eur J Med Chem. 2020 Apr 1;191:112154.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA