TK-129

Cat. No.: HY-151483

CAS No.: 3031476-73-7

Molecular Formula: $C_{15}H_{23}N_5O_2$

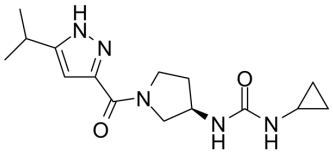
Molecular Weight: 305.38

Target: Histone Demethylase

Pathway: Epigenetics

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (327.46 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2746 mL	16.3730 mL	32.7461 mL
	5 mM	0.6549 mL	3.2746 mL	6.5492 mL
	10 mM	0.3275 mL	1.6373 mL	3.2746 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 (8.19 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (8.19 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.19 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

TK-129 is an orally active, low-toxicity, potent KDM5B inhibitor (with high affinity; IC_{50}=44 nM). TK-129 exerts cardioprotective effects by inhibiting KDM5B and blocking the KDM5B-associated Wnt pathway. TK-129 reduces ang II-induced activation of cardiac fibroblasts in vitro and reduces isoprenaline-induced myocardial remodelling and fibrosis in vivo. TK-129 can be used in studies of cardiovascular disease[1].

IC_{50} & Target

KDM5

44 nM (IC_{50})

In Vitro

TK-129 mediates inhibition of KDM5B activity significantly reduces the activation, migration, and proliferation of myofibroblasts induced by Ang II in vitro[1].
TK-129 (10 μM; 48 h) shows low cytotoxicity in NRCFs and NRCMs[1].
TK-129 (0.1, 0.2, 0.3, 0.4, 0.5 μM; 48 h) can engage toand inhibit KDM5B activity in NRCFs[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Cytotoxicity Assay[1]

Cell Line:	NRCFs and NRCMs
Concentration:	10 μM
Incubation Time:	48 h
Result:	Exhibited the cell survival rates were almost more than 90%.

Western Blot Analysis[1]

Cell Line:	NRCFs
Concentration:	0.1, 0.2, 0.3, 0.4, 0.5 μM
Incubation Time:	48 h
Result:	Increased the expression level of KDM5B substrate H3K4me3 protein in a concentration-dependent manner.

In Vivo

TK-129 (2 g/kg; p.o.; single) shows good bio-safety in mice[1].
TK-129 (50 mg/kg; p.o.; twice daily for 24 days) effectively reduces isoproterenol-induced pathological myocardial remodeling in vivo[1].
TK-129 (2 or 10 mg/kg; i.v. or p.o.; single) demonstrates favorable PK properties in vivo[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Wild C57BL/6 mice (8 to 10-week-old; half male and half female)[1].
Dosage:	2 g/kg
Administration:	Oral gavage, single.
Result:	Exhibited all mice in the acute toxicity group survived and gained weight normally, after 2 weeks.

Animal Model:	C57BL/6 mice (isoproterenol (ISO)-induced)[1].
Dosage:	50 mg/kg
Administration:	Oral gavage, twice daily for 24 days.
Result:	Alleviated myocardial remodeling induced by ISO in vivo.

Animal Model:	Male SD Rats (223.5-265.1 g)[1].
Dosage:	2 mg/kg (for i.v.); 10 mg/kg (for p.o.).
Administration:	Intravenous injection or oral gavage; single.

Result:

Pharmacokinetic Parameters of TK-129 in Male SD Rats[1].

	PO (10 mg/kg)	IV (2 mg/kg)
CL (L/h/kg)	9.9	4.2
V_{ss} (L/kg)	33.4	2.7
$T_{1/2}$ (h)	2.4	0.4
T_{max} (h)	0.4	-
C_{max} (ng/mL)	709.7	1229.1
AUC_{0-24} (ng/mL•h)	1038.2	479.6
F (%)	42.37	-

REFERENCES

[1]. Tang K, et al. Discovery of Novel Pyrazole-Based KDM5B Inhibitor TK-129 and Its Protective Effects on Myocardial Remodeling and Fibrosis. J Med Chem. 2022 Sep 16.

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