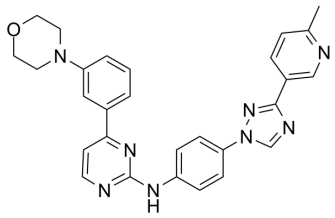
SR-3306

Cat. No.:	HY-12829
CAS No.:	1128096-91-2
Molecular Formula:	$C_{28}H_{26}N_8O$
Molecular Weight:	490.56
Target:	JNK
Pathway:	MAPK/ERK Pathway
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 (254.81 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0385 mL	10.1924 mL	20.3849 mL
5 mM	0.4077 mL	2.0385 mL	4.0770 mL
10 mM	0.2038 mL	1.0192 mL	2.0385 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 (4.24 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

SR-3306 is a selective, potent, highly brain penetrant JNK inhibitor.

IC_{50} & Target

JNK

In Vitro

The effect of SR-3306 or Tat-Sab on cell viability in response to oxidative stress is measured by an MTT assay. H9c2 cells treated with 100 μM H_2O_2/$FeSO_4$ are ~40% viable, whereas the addition of 500 nM SR-3306 or 500 nM SR3562 to cells treated with 100 μM H_2O_2/$FeSO_4$ increases viability to ~90%, and the addition of 10 μM Tat-Sab peptide to cells treated with 100 μM H_2O_2/$FeSO_4$ increases viability to ~70% compared with 98% viability in untreated cells. Similar results are found for primary human cardiomyocytes [2].

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

In Vivo

Administration of SR-3306 [10 mg/kg/day (s.c.) for 14 days] increases the number of tyrosine hydroxylase immunoreactive

	(TH^+) neurons in the SNpc by 6-fold and reduces the loss of the TH^+ terminals in the striatum relative to the corresponding side of 6-OHDA-lesioned rats that receive only vehicle ($p<0.05$). In addition, SR-3306 [10 mg/kg/day (s.c.) for 14 days] decreases d-amphetamine-induced circling by 87% compared to 6-hydroxydopamine (6-OHDA)-lesioned animals given vehicle. Steady-state brain levels of SR-3306 at day 14 are 347 nM, which is approximately 2-fold higher than the cell-based IC_{50} for this compound. Finally, immunohistochemical staining for phospho-c-jun (p-c-jun) reveals that SR-3306 [10 mg/kg/day (s.c.) for 14 days] produces a 2.3-fold reduction of the number of immunoreactive neurons in the substantia nigra pars compacta (SNpc) relative to vehicle treated rats[1]. In lean mice, intraperitoneal (i.p.) or intracerebroventricular (i.c.v.) administration of SR-3306 reduces food intake and body weight. Moreover, i.p. and i.c.v. administrations of SR11935 exert similar anorectic effects as SR3306, which suggests JNK2 or JNK3 mediates aspect of the anorectic effect by pan-JNK inhibition. Furthermore, daily i.p. injection of SR-3306 (7 days) prevents the increases in food intake and weight gain in lean mice upon high-fat diet feeding, and this injection paradigm reduced high-fat intake and obesity in diet-induced obese (DIO) mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	H9c2 cells and primary human cardiomyocytes are grown under normal cell culture conditions (37 °C and 5% CO_2) in DMEM supplemented with 10% fetal bovine serum and penicillin/streptomycin. To assure that the cells are actively growing, only cells at ~80% confluency and between passages 5 and 15 are used in our experiments. H9c2 cells and primary human cardiomyocytes are exposed to 500 nM SR-3306, 500 nM SR-3562, 0.01% DMSO vehicle control, 10 μM Tat-Sab_{KIM1}, and 10 μM Tat-scramble for 30 min prior to the addition of stress. To induce oxidative stress and mitochondrial dysfunction in H9c2 cells and primary human cardiomyocytes, 100 μM hydrogen peroxide (H_2O_2)/$FeSO_4$ or 100 μM hydrogen peroxide (H_2O_2)/$FeSO_4$ is added directly to the media of the cells. The cells are exposed to H_2O_2/$FeSO_4$ for the times indicated in the experiments[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][3]	Rats[1] Four Sprague-Dawley rats are used. SR-3306 is dosed at 2.5 or 10 mg/kg in subcutaneous minipumps at a rate of 5 μL/h, and after 24 h on days 1, 2, 3, 4, 6, 7, 8, 9, 10, 13, and 14 blood, and day 14 brain are collected. Plasma is generated, and the samples are frozen at -80 °C. The plasma and brain are mixed with Acetonitrile (1:5 v/v or 1:5 w/v, respectively). The brain sample is sonicated with a probe tip sonicator to break up the tissue, and samples are analyzed for compound levels by LC-MS/MS. Plasma compound levels are determined against standards made in plasma and brain levels against standards made in blank brain matrix[1]. Mice[3] Male, lean or DIO C57BL/6 mice are used. The mice are trained to scheduled, daily, 2-hour water access during the light for 2 weeks. On the first day of the conditioned taste aversion (CTA) test, the trained mice are given a novel 0.15% saccharin solution to drink for the first 50 minutes, and are then given an i.p. injection of SR-3306 (30 mg/kg or 60 mg/kg) or the vehicle. The injected mice are then provided water for the remaining 70 min. The next day, the mice are allowed to choose between water and 0.15% saccharin for 50 min. Fluid consumption is calculated[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Crocker CE, et al. JNK Inhibition Protects Dopamine Neurons and Provides Behavioral Improvement in a Rat 6-hydroxydopamine Model of Parkinson's Disease. ACS Chem Neurosci. 2011 Apr 20;2(4):207-212.

[2]. Chambers JW, et al. Inhibition of JNK mitochondrial localization and signaling is protective against ischemia/reperfusion injury in rats. J Biol Chem. 2013 Feb 8;288(6):4000-11.

[3]. Gao S, et al. Pharmacological Inhibition of c-Jun N-terminal Kinase Reduces Food Intake and Sensitizes Leptin's Anorectic Signaling Actions. Sci Rep. 2017 Feb 6;7:41795.

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

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