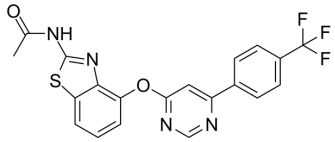
AMG 517

Cat. No.:	HY-10634
CAS No.:	659730-32-2
Molecular Formula:	$C_{20}H_{13}F_3N_4O_2S$
Molecular Weight:	430.4
Target:	TRP Channel
Pathway:	Membrane Transporter/Ion Channel; Neuronal Signaling
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 : 41.67 mg/mL (96.82 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3234 mL	11.6171 mL	23.2342 mL
	5 mM	0.4647 mL	2.3234 mL	4.6468 mL
	10 mM	0.2323 mL	1.1617 mL	2.3234 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 (5.81 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.81 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AMG 517 is a potent and selective vanilloid receptor-1 (TRPV1) antagonist with an IC_{50} of 0.5 nM.

IC_{50} & Target

IC50: 0.5 nM (TRPV1)[1]

In Vitro

AMG 517 retains potency in the capsaicin- and acid-mediated assays with IC_{50} values of 0.9 and 0.5 nM[1]. AMG 517 inhibits capsaicin, pH 5, and heat-induced $^{45}Ca^{2+}$ uptake into cells expressing TRPV1 with IC_{50} values of 1 to 2 nM. AMG 517 blocks capsaicin-, proton-, and heat-induced inward currents in TRPV1-expressing cells similarly. AMG 517 inhibits native TRPV1 activation by capsaicin in rat dorsal root ganglion neurons with an IC50 value of 0.68 ± 0.2 nM. AMG 517 is a competitive antagonist of both rat and human TRPV1 with dissociation constant (Kb) values of 4.2 and 6.2 nM, respectively[2].

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

In Vivo	AMG 517 is shown to be effective in a rodent "on-target" biochemical challenge model (capsaicin-induced flinch, ED_{50}=0.33 mg/kg p.o.) and is antihyperalgesic in a model of inflammatory pain (CFA-induced thermal hyperalgesia, MED=0.83 mg/kg, p.o.)[1].The minimally effective dose is 0.3 mg/kg for AMG 517 and the corresponding plasma concentration is 90 ng/mL. Oral administration of AMG 517 reverses established thermal hyperalgesia in a dose-dependent manner at 21 h after CFA injection. AMG 517 causes transient hyperthermia in rodents, dogs, and monkeys. AMG 517 induces hyperthermia in a steep dose-dependent manner, with 0.3, 1, and 3 mg/kg associated with 0.5, 0.6, and 1.6°C increases in body temperature, respectively. Body temperatures of rats treated with all doses of AMG 517 return to baseline within 10 to 20 h[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2]	Rats: After multiple days of full habituation to the testing equipment and paradigm, CFA-induced thermal hyperalgesia is evaluated by measuring paw withdrawal latencies in male Sprague-Dawley rats. Twenty-one hours after CFA injection (50 µL of 0.1%), animals are dosed (p.o.) with AMG 517 or AMG8163 at a dose range of 0.001 to 30 mg/kg in a volume of 5 mL/kg. Two hours after drug dosing (23 h after CFA injection), paw withdrawal latencies are measured using modified Hargreaves hot boxes by investigators fully blinded to treatment conditions[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- EMBO Rep. 2016 Oct;17(10):1422-1430.
- Front Pharmacol. 2022 Feb 23;13:816133.
- Front Pharmacol. 23 February 2022.
- Biophys J. 2017 Jan 10;112(1):87-98.

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REFERENCES

[1]. Doherty EM, et al. Novel vanilloid receptor-1 antagonists: 2. Structure-activity relationships of 4-oxopyrimidines leading to the selection of a clinical candidate. J Med Chem. 2007 Jul 26;50(15):3515-27.

[2]. Gavva NR, et al. Repeated administration of vanilloid receptor TRPV1 antagonists attenuates hyperthermia elicited by TRPV1 blockade. J Pharmacol Exp Ther. 2007 Oct;323(1):128-37.

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