GSK2193874

Cat. No.: HY-100720

CAS No.: 1336960-13-4

Molecular Formula: $C_{37}H_{38}BrF_3N_4O$

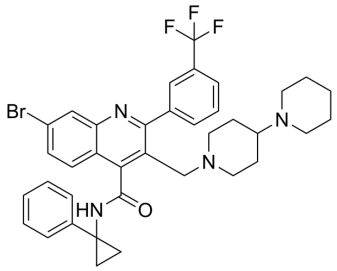
Molecular Weight: 691.62

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 : 100 mg/mL (144.59 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4459 mL	7.2294 mL	14.4588 mL
	5 mM	0.2892 mL	1.4459 mL	2.8918 mL
	10 mM	0.1446 mL	0.7229 mL	1.4459 mL

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

In Vivo

1. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (3.61 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (3.01 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.01 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK2193874 is an orally active, potent, and selective TRPV4 antagonist with IC_{50}s of 2 nM and 40 nM for rTRPV4 and hTRPV4 [1].

IC_{50} & Target

IC50: 2 nM (rTRPV4), 40 nM (hTRPV4)[1]

In Vitro

GSK2193874 is profiled against TRP channels and is selective against TRPV1, TRPA1, TRPC3, TRPC6, and TRPM8 (IC_{50}>25 μM) [1]. GSK2193874 is a selective, orally active TRPV4 blocker that inhibits Ca^{2+} influx through recombinant TRPV4 channels and

	native endothelial TRPV4 currents. In whole-cell patch-clamp studies, GSK2193874 inhibits activation of recombinant TRPV4 currents when applied to the extracellular solution at 3 nM and above but is ineffective at up to 10 μM when applied to the inside of the cell by inclusion in the intracellular pipette solution[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The pharmacokinetic (PK) properties for GSK2193874 are evaluated in both rat and dog and found to have half-lives and oral exposure suitable for oral dosing in chronic animal models (Rat PK: iv CL=7.3 mL/min/kg, po $t_{1/2}$=10 h, %F=31. Dog PK: iv CL=6.9 mL/min/kg, po $t_{1/2}$=31 h, %F=53). In addition, GSK2193874 shows no blood pressure or heart rate effect in rats when dose up to 30 mg/kg. GSK2193874 is the first-in-class orally bioavailable TRPV4 inhibitor that demonstrated ability to improve pulmonary functions in a number of heart failure models[1]. GSK2193874 shows low clearance (7.3 mL/min/kg) and good rat oral bioavailability (31%)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2]	Rats[2] Adult male Sprague-Dawley rats (n=7 to 8 per group) are treated with vehicle (6% Cavitron) or GSK2193874 (30 mg/kg per day) via oral gavage for at least 4 days before osmotic challenges. Rats undergo acute and chronic hyper- and hypo-osmotic challenges. Sprague-Dawley rats are administered vehicle (0.9% NaCl, 25 mL/kg), NSC 269420 (30 mg/kg), or hydrochlorothiazide (30 mg/kg) via oral gavage. Urine is then collected over 4 hours followed by blood sampling. Rats recover for 4 days and then receive GSK2193874 (30 mg/kg per day oral gavage) for 5 days before repeating the diuretic challenge. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Autophagy. 2021 Nov;17(11):3592-3606.
- J Nanobiotechnology. 2022 Jul 6;20(1):314.
- Acta Pharmacol Sin. 2022 Sep 23.
- J Leukoc Biol. 2023 May 26;qiad063.
- J Ethnopharmacol. 2022 Feb 11;290:115105.

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REFERENCES

[1]. Cheung M, et al. Discovery of GSK2193874: An Orally Active, Potent, and Selective Blocker of Transient Receptor Potential Vanilloid 4. ACS Med Chem Lett. 2017 Mar 20;8(5):549-554.

[2]. Thorneloe KS, et al. An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. Sci Transl Med. 2012 Nov 7;4(159):159ra148.

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