产品名称：GSK2193874
产品别名：GSK2193874

生物活性：

Description	GSK2193874 is an orally active, potent, and selective TRPV4 antagonist with IC_{50} of 2 nM and 40 nM for rTRPV4 and hTRPV4.
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].
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].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL** (**144.59 mM**) **H_2O : < 0.1 mg/mL** (insoluble) * "≥" means soluble, but saturation unknown.

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.08 mg/mL (3.01 mM); Clear solution

此方案可获得 ≥ 2.08 mg/mL (3.01 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 20.8 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

	2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.08 mg/mL (3.01 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (3.01 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 20.8 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Animal Administration	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), Furosemide (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.
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.