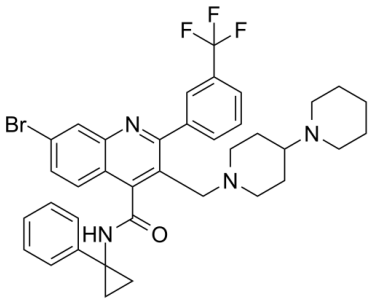
Data Sheet

Product Name:	GSK2193874
Cat. No.:	CS-7612
CAS No.:	1336960-13-4
Molecular Formula:	C37H38BrF3N4O
Molecular Weight:	691.62
Target:	TRP Channel
Pathway:	Membrane Transporter/Ion Channel; Neuronal Signaling
Solubility:	DMSO : 100 mg/mL (144.59 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

GSK2193874 is an orally active, potent, and selective **TRPV4** antagonist with **IC_{50}** of 2 nM and 40 nM for **rTRPV4** and **hTRPV4**. IC50 & 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].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: GSK2193874 is prepared in vehicle (6% Cavitron) (Rat)[2].[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), 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.

CAIndexNames:

4-Quinolinecarboxamide, 3-([1,4'-bipiperidin]-1'-ylmethyl)-7-bromo-N-(1-phenylcyclopropyl)-2-[3-(trifluoromethyl)phenyl]-

SMILES:

O=C(C1=C(CN2CCC(N3CCCCC3)CC2)C(C4=CC=CC(C(F)(F)F)=C4)=NC5=CC(Br)=CC=C15)NC6(C7=CC=CC=C7)CC6

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

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