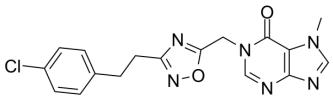
AM-0902

Cat. No.:	HY-108329
CAS No.:	1883711-97-4
Molecular Formula:	$C_{17}H_{15}ClN_6O_2$
Molecular Weight:	370.79
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 : 150 mg/mL (404.54 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6969 mL	13.4847 mL	26.9694 mL
	5 mM	0.5394 mL	2.6969 mL	5.3939 mL
	10 mM	0.2697 mL	1.3485 mL	2.6969 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 (6.74 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.74 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.74 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AM-0902 is a potent, selective transient receptor potential A1 (TRPA1) antagonist with IC_{50}s of 71 and 131 nM for rTRPA1 and hTRPA1, respectively.

IC_{50} & Target

IC50: 71 nM (rTRPA1), 131 nM (hTRPA1)[1]

In Vitro

AM-0902 is a potent, selective antagonist of TRPA1 with IC_{50}s of 71 and 131 nM for rTRPA1 and hTRPA1, respectively. AM-0902 is highly permeable (average P_{app}=44.5 μcm/s in MDCK cells), an unlikely substrate for P-gp (efflux ratio=1.3 in P-gp

	overexpressing MDCK cells), and demonstrates good solubility (PBS pH 7.4: 226 μM, SIF: 248 μM). AM-0902 shows good selectivity over other TRP channels, as no activity is observed against human TRPV1 or TRPV4, or rat TRPV1, TRPV3, or TRPM8, at concentrations up to 10 μM. AM-0902 inhibits $^{45}Ca^{2+}$ flux upon activation of rat TRPA1 with methylglyoxal with an IC_{50} of 0.019 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AM-0902 is a potent, selective antagonist of TRPA1 in vivo. AM-0902 has moderate terminal elimination half-life ($t_{1/2}$=0.6 h and 2.8 h for rat (0.5 mg/kg, iv), rat (30 mg/kg, oral)). A dose-dependent reduction of allyl isothiocyanate (AITC)-induced flinching is observed for AM-0902, with a significant reduction in flinching observed postdosing of 10 and 30 mg/kg. The unbound plasma concentrations (C_u) at 1 h for the 1, 3, 10, and 30 mg/kg doses are 0.051±0.024 (n=8), 0.19±0.11 (n=8), 0.58±0.35 (n=8), and 2.2±0.40 (n=8) μM, covering the in vitro rat TRPA1 $^{45}Ca^{2+}$ IC_{50} at 0.72, 2.7, 8.2, and 30.3 fold, respectively. A good exposure-response relationship is observed in this target coverage model. An unbound in vivo IC_{50} of 0.35 μM, which is in good agreement with the in vitro rat TRPA1 $^{45}Ca^{2+}$ IC_{50}, and unbound in vivo IC_{90} of 1.7 μM are determined. It is noteworthy that at a dose of 30 mg/kg, AM-0902 engages TRPA1 at concentrations that exceed the in vivo IC_{90}, making it a useful tool for exploration of in vivo models of acute pain[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	MDCK cells are generated and maintained for the TRPA1 calcium flux assays. On the day of assay, culture media is removed and cells are incubated for 10 min at room temperature (RT) with 50 μL of AM-0902 (compound 27) in AM-0902 dilution buffer [HBSS containing 1 mM HEPES+0.1 mg/mL BSA] at final concentrations (2.0 nM to 40 μM, 1:3 ratio), followed by another 3 min incubation at RT. The reaction mixture is aspirated, and cells are washed three times with phosphate buffer saline (PBS) containing 0.1 mg/mL BSA. Radioactivity is measured using a TopCount microplate scintillation counter. The activation of TRPA1 is measured by the cellular uptake of radioactive calcium[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats[1] Rats are dosed orally with either vehicle (2% HPMC/1% Tween-80) or AM-0902 at 1, 3, 10, or 30 mg/kg. After 1 h, one left ventral hind paw is injected with the TRPA1 agonist AITC (0.1%). AM-0902 is also given by an intravenous (IV) injection to rats (0.5 mg/kg)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Schenkel LB, et al. Optimization of a Novel Quinazolinone-Based Series of Transient Receptor Potential A1 (TRPA1)Antagonists Demonstrating Potent in Vivo Activity. J Med Chem. 2016 Mar 24;59(6):2794-809.

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