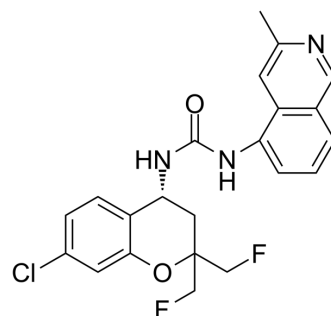


A-1165442

Cat. No.:	HY-12428		
CAS No.:	1221443-94-2		
Molecular Formula:	C ₂₂ H ₂₀ ClF ₂ N ₃ O ₂		
Molecular Weight:	431.86		
Target:	TRP Channel		
Pathway:	Membrane Transporter/Ion Channel; Neuronal Signaling		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (231.56 mM)
 H₂O : < 0.1 mg/mL (insoluble)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
	1 mM	2.3156 mL	11.5778 mL	23.1557 mL
	5 mM	0.4631 mL	2.3156 mL	4.6311 mL
	10 mM	0.2316 mL	1.1578 mL	2.3156 mL

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

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: ≥ 2.5 mg/mL (5.79 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 2.5 mg/mL (5.79 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

A-1165442 is a potent, competitive and orally available TRPV1 antagonist with an IC₅₀ of 9 nM for human TRPV1.

IC₅₀ & Target

IC₅₀: 9 nM (human TRPV1)^[1]

In Vitro

A-1165442 displays potent, competitive antagonism at recombinant human TRPV1 activated by capsaicin (IC₅₀=9 nM) and incomplete blockade of acid-evoked response (62% block at 30 μM). A-1165442 possesses excellent selectivity (>100-fold) versus other members of the TRP family (TRPA1, TRPM8, TRPV2, TRPV3) and other receptors expressed in peripheral sensory neurons including P2X2/3, Cav2.2, Nav channels, and KCNQ2/3. A-1165442 shows minimal cross-reactivity upon evaluation

(10 μM) in a broad screening panel (n=74, CEREP) of cell-surface receptors, ion channels, and enzymes^[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

A-1165442 exhibits excellent pharmacological selectivity, has a favorable pharmacokinetic profile, and demonstrates good efficacy against osteoarthritis pain in rodents. Oral administration of A-1165442 prevents capsaicin-induced nocifensive behaviors in rats, with an ED_{50} of 9.5 $\mu\text{mol}/\text{kg}$ corresponding to plasma concentration of 420 ng/mL (970 nM). A single dose of A-1165442 produces a robust effect on grip force, with an ED_{50} of 35 $\mu\text{mol}/\text{kg}$ measured 1 h postdosing. Repeated dosing of A-1165442 results in an increase in potency relative to acute analgesic efficacy. No significant changes in core body temperature is observed in conscious rats dosed with A-1165442 and this temperature-neutral profile is maintained in conscious dogs^[1].

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

PROTOCOL

Animal Administration ^[1]

Dogs: Male beagle dogs are instrumented with telemetry transmitters capable of monitoring core body temperature and then allowed to recover. Dosing is initiated at time zero, with dogs receiving a single oral dose of vehicle, compound 1 at (30 $\mu\text{mol}/\text{kg}$), or A-1165442 (100 $\mu\text{mol}/\text{kg}$); n=4–6 per group. Measurements are recorded every 5 min for the duration of the study, then averaged to 15 min and 1 h intervals. Temperature signals are transmitted as radio signals by each implanted transmitter to a receiver placed on the cage and interfaced with a desktop personal computer^[1].

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

CUSTOMER VALIDATION

- Patent. US20200147014A1

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REFERENCES

[1]. Voight EA, et al. Discovery of (R)-1-(7-chloro-2,2-bis(fluoromethyl)chroman-4-yl)-3-(3-methylisoquinolin-5-yl)urea (A-1165442): a temperature-neutral transient receptor potential vanilloid-1 (TRPV1) antagonist with analgesic efficacy. *J Med Chem.* 2014 Sep 11;57(17):7412-24.

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

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