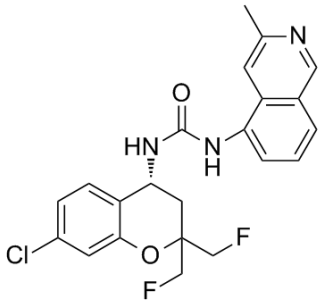
A-1165442

Cat. No.:	HY-12428
CAS No.:	1221443-94-2
Molecular Formula:	$C_{22}H_{20}ClF_2N_3O_2$
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)

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	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

1. 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
2. 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 IC_{50} of 9 nM for human TRPV1.

IC_{50} & Target

IC50: 9 nM (human TRPV1)[1]

In Vitro

A-1165442 displays potent, competitive antagonism at recombinant human TRPV1 activated by capsaicin (IC_{50}=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 μmol/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 μmol/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 μmol/kg), or A-1165442 (100 μmol/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.

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