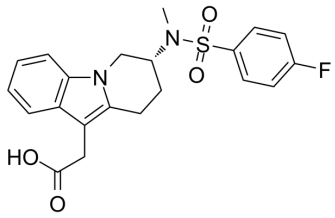
MK-7246

Cat. No.:	HY-15853
CAS No.:	1218918-62-7
Molecular Formula:	$C_{21}H_{21}FN_2O_4S$
Molecular Weight:	416.47
Target:	Prostaglandin Receptor
Pathway:	GPCR/G Protein
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 : 300 mg/mL (720.34 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4011 mL	12.0057 mL	24.0113 mL
	5 mM	0.4802 mL	2.4011 mL	4.8023 mL
	10 mM	0.2401 mL	1.2006 mL	2.4011 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: 3.75 mg/mL (9.00 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 3.75 mg/mL (9.00 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 3.75 mg/mL (9.00 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

MK-7246 is a potent and selective CRTH2 antagonist with a K_i of 2.5±0.5 nM.

IC_{50} & Target

DP	TP
2.5 nM (Ki)	3804 nM (Ki)

In Vitro

The affinity and selectivity of MK-7246 for human CRTH2 and recombinant human prostanoid receptors is determined by equilibrium competition analysis using the relevant radioligands and cell membranes expressing the various receptors. MK-

	7246 competes for [^{3}H]PGD_2 specific binding to cell membranes expressing recombinant human CRTH2 with high-affinity (K_i, 2.5 nM). MK-7246 displays a relatively high selectivity for CRTH2 with an affinity 149-fold lower for the DP receptor (K_i, 373±96 nM) and ≥1500-fold lower for the other prostanoid receptors (K_i, 7668±2169 nM for EP_2, 3804±1290 nM for TP). MK-7246 is also tested in a panel of 157 enzyme and receptor assays at concentrations up to 100 μM and small but significant activity is detected only on phosphodiesterase 1 (PDE1, IC_{50}=33.2 μM) and MAPK3 (ERK1, IC_{50}=49.4 μM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Whether the inhibition of a clinically-relevant mechanism of allergic lung inflammation such as CRTH2 will lead to a suppression of inflammatory responses is investigated in A. alternata challenged Brown Norway rats (n=8 per group). Mast cell derived production of Prostaglandin D_2 (PGD_2) is believed to be a prime mediator of allergic inflammation. Since CRTH2 plays an important role in the early aspects of the allergic inflammation cascade, the effect of the CRTH2 antagonist is examined on A. alternate elicited pulmonary inflammatory responses. CRTH2 inhibitor MK-7246 is orally administered 1 h before and 23 h post-intratracheal instillation of the A. alternata. MK-7246 produces a dose dependent decrease in the number of eosinophils with a maximal inhibition of 74±5% in the 100 mg/kg group (P<0.05), IL-5 (80±12%) and IL-13 (76±14%) cytokines levels (P<0.05) [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The binding kinetics of [^{3}H]MK-7246 (specific activity, 41 Ci/mmol) at human CRTH2 is characterized using recombinant HEK293E cell membranes. The radioligand binding experimental condition for CRTH2 as follows: the incubation mixture contains 10 mM $MgCl_2$ instead of $MnCl_2$, 10 nM [^{3}H]MK-7246, and 1.25 μg of membrane protein. Total binding represents 10% of the radioligand adds to the incubation media, and specific binding at equilibrium corresponded to 85 to 95% of the total binding. The membranes are first incubated with [^{3}H]MK-7246 for 120 min in the absence (total binding) or presence (nonspecific binding) of 10 μM MK-7246. To one series of total binding incubation tubes, 10 μM MK-7246 or 100 μM PGD_2 is added to initiate dissociation of the radioligand from the receptor, and the reaction is left to proceed for up to 300 min. The samples are then harvested and processed as detailed above. The association and dissociation kinetic data analysis is done by nonlinear regression curve-fitting using Prism software to determine the observed on rate (K_{obs}) and dissociation rate (k_{off}) constants, and $t_{1/2}$ of on and off rates[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Rats[2] Intratracheal Budesonide is dosed 1 h prior to and 23 h post the A. alternate intratracheal dose while oral Budesonide (3 mg/kg) is administered 2 h before and 22 h post the A. alternata extract instillation. An intratracheally dosed Budesonide is prepared. MK-7246 (3, 10, 30 and 100 mg/kg) is administered orally 1 h before and 23 h post an A. alternata extract instillation in order to examine the effect of the CRTH2 antagonist on A. alternata elicited pulmonary inflammatory responses. Budesonide dosed orally is used as a positive control in both experiments. The animals are lightly anesthetized with 3% Isoflurane (supplemented with 100% oxygen), either 2 h following an oral dosing or 1 h following an intratracheal dosing. The animals are also secured on a rodent work stand to facilitate the localization of the larynx and tracheal openings. The microsprayer needle is inserted into the trachea and 0.1 mL of 10,000 μg/mL (total of 1000 μg) A. alternata extract is administered using a microsprayer. The animals are observed until they recover from anesthesia and then return to their cages and allow food and water ad libitum. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Gervais FG, et al. Pharmacological characterization of MK-7246, a potent and selective CRTH2 (chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells) antagonist. Mol Pharmacol. 2011 Jan;79(1):69-76.

[2]. Gil MA, et al. Anti-inflammatory actions of Chemoattractant Receptor-homologous molecule expressed on Th2 by the antagonist MK-7246 in a novel rat model of

Alternaria alternata elicited pulmonary inflammation. Eur J Pharmacol. 2014 Nov 15;743:106-16.

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