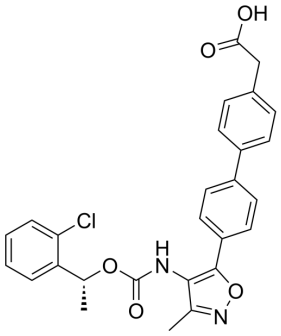
AM966

Cat. No.:	HY-15277
CAS No.:	1228690-19-4
Molecular Formula:	$C_{27}H_{23}ClN_2O_5$
Molecular Weight:	490.93
Target:	LPL 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 : 100 mg/mL (203.70 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0370 mL	10.1848 mL	20.3695 mL
	5 mM	0.4074 mL	2.0370 mL	4.0739 mL
	10 mM	0.2037 mL	1.0185 mL	2.0370 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (20.37 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (5.09 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.09 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AM966 is a high affinity, selective, oral LPA_1-antagonist, inhibits LPA-stimulated intracellular calcium release (IC_{50}=17 nM).

IC_{50} & Target

LPA_1[1]

In Vitro

AM966 is a potent, selective, orally bioavailable LPA_1 receptor antagonist. AM966 inhibits LPA_1-mediated chemotaxis of human A2058 melanoma cells (IC_{50}=138±43 nM), IMR-90 human lung fibroblasts (IC_{50}=182±86 nM) and CHO mLPA_1 cells (IC_{50} =469±54 nM)[1]. LPA-induced ERK1/2 activation is completely blocked by AM966 (100 nM), which selectively antagonizes LPA

	$_1$ over LPA_{2-5}, with an IC_{50} value of 3.8±0.4 nM. Pre-treatment with AM966 (100 nM) completely blocks ERK1/2 phosphorylation induced by Mianserin[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AM966 (30 mg/kg, BID) reduces vascular leakage, inflammation and lung injury and inflammation in a 3 day Bleomycin (HY-108345) model. AM966 inhibits lung fibrosis, maintains mouse body weight and decreases lung inflammation 14 days after Bleomycin lung injury. AM966 reduces vascular leakage, tissue injury and pro-fibrotic cytokine production in the 14 day Bleomycin study. AM966 demonstrates greater efficacy compared to Pirfenidone (HY-B0673) in the 14 day Bleomycin model. AM966 decreases mortality and fibrosis at late time points after Bleomycin injury[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	CHO-K1 cells are grown to 80% confluency in 12-well plates, serum-starved for 24 h and incubated in serum-free medium with AM966. After 21 h, [^{3}H]thymidine (0.5 μCi/well) is added and the incubation is continued for 3 h. The medium is then removed, and the cells are placed on ice and washed twice with 1 mL of ice-cold PBS containing 5% trichloroacetic acid. Cells are solubilized and [^{3}H]thymidine incorporation is determined by liquid scintillation counting. Assays are performed in triplicate[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] The oral exposure of AM966 is determined in fasted mice. Animals received AM966 (10 mg/kg) in vehicle (water) by oral gavage and are then killed by CO_2 inhalation at 1, 2, 4, 8 and 24 h post dose (n=2 animals per time point for each test compound). Blood (approximately 300 μL) is collected via cardiac puncture into EDTA-containing tubes and centrifuged at 1450×g for 10 min. The plasma is removed and analysed for AM966 content by liquid chromatography-mass spectrometry (LCMS). Briefly, known amounts of AM966 are added to thawed mouse plasma to yield a concentration range from 0.8 to 4000 ng/mL. Mouse plasma samples are precipitated using acetonitrile (1:4, v:v) containing the internal standard buspirone. A 10 μL aliquot of the analyte mixture is injected using a Leap PAL autosampler. Analyses are performed using an Agilent Zorbax SB-C8 column (2.1×50 mm; 5 μm) linked to a Shimadzu LC-10AD VP with SCL-10A VP system controller. Tandem mass spectrometric detection is carried out on a PE Sciex API3200 in the positive ion mode (ESI) by multiple reaction monitoring. The calibration curves are constructed by plotting the peak-area ratio of analysed peaks against known concentrations. The lower limit of quantitation is 0.8 ng/mL. The data are subjected to linear regression analysis with $1/x^2$weighting. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Metab. 2022 Mar 10;S1550-4131(22)00083-3.
- Autophagy. 2022 Feb 27;1-22.
- Cell Commun Signal. 2023 Sep 25;21(1):257.
- Neuropsychopharmacol Rep. 2019 Sep;39(3):156-163.
- Apoptosis. 2019 Jun;24(5-6):478-498.

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REFERENCES

[1]. Swaney, JS, et al. A novel, orally active LPA1 receptor antagonist inhibits lung fibrosis in the mouse bleomycin model. Br J Pharmacol. 2010 Aug;160(7):1699-713.

[2]. Olianas MC, et al. Antidepressants activate the lysophosphatidic acid receptor LPA(1) to induce insulin-like growth factor-I receptor transactivation, stimulation of ERK1/2 signaling and cell proliferation in CHO-K1 fibroblasts. Biochem Pharmacol. 2015 Jun 15;95(4):311-23.

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