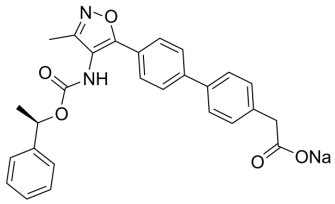
AM095

Cat. No.:	HY-16039
CAS No.:	1345614-59-6
Molecular Formula:	$C_{27}H_{23}N_2NaO_5$
Molecular Weight:	478.47
Target:	LPL Receptor
Pathway:	GPCR/G Protein
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 83.33 mg/mL (174.16 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0900 mL	10.4499 mL	20.8999 mL
5 mM	0.4180 mL	2.0900 mL	4.1800 mL
10 mM	0.2090 mL	1.0450 mL	2.0900 mL

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

In Vivo

1. Add each solvent one by one: Saline
   Solubility: 5 mg/mL (10.45 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.35 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.35 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.35 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AM095 is a selective LPA_1 receptor antagonist. The IC_{50} for AM095 antagonism of LPA-induced calcium flux of human or mouse LPA_1-transfected CHO cells is 0.025 and 0.023 μM, respectively.

IC_{50} & Target

LPA_1 receptor[1]

In Vitro

AM095 is a potent LPA_1 receptor antagonist because it inhibits GTPγS binding to Chinese hamster ovary (CHO) cell membranes overexpressing recombinant human or mouse LPA_1 with IC_{50} values of 0.98 and 0.73 μM, respectively. AM095

	inhibits LPA-driven chemotaxis of CHO cells overexpressing mouse LPA_1 (IC_{50}=778 nM) and human A2058 melanoma cells (IC_{50}=233 nM). The IC_{50} of AM095 in the human LPA_1 GTPγS binding assay is comparable with that of our previously published compound AM966 (IC_{50}=0.98±0.17 μM) and the Debio-0719 compound (IC_{50}=0.60±0.04 μM)[1]. AM095 inhibits the LPA-induced calcium flux of CHO cells stably transfected with human or mouse LPA_1. The IC_{50} for AM095 antagonism of LPA-induced calcium flux of human or mouse LPA_1-transfected CHO cells is 0.025 and 0.023 μM, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AM095 has high oral bioavailability and a moderate half-life and is well tolerated at the doses tested in rats and dogs after oral and intravenous dosing. After oral (10 mg/kg) dosing in rats, AM095 plasma concentrations peaked at 2 h with a C_{max} of 41 μM, thereafter decreasing to 10 nM by 24 h. After intravenous (2 mg/kg) dosing, a C_{max} of 12 μM is observed within 15 min, which also decreased to approximately 10 nM by 24 h, yielding a $t_{1/2}$ of 1.79 h. In dogs, a single oral dose of 5 mg/kg yielded a peak plasma concentration of 21 μM within 15 min of dosing, which then decreased to 10 nM by 24 h. In contrast, an intravenous dose of 2 mg/kg resulted in a C_{max} of 11 μM within 15 min and decreased to 15 nM by 8 h, yielding a $t_{1/2}$ of 1.5 h [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Known amounts of AM095 (diluted in DMSO) or vehicle (DMSO) are added to 25 to 40 μg of $hLPA_1$/CHO or $mLPA_1$/CHO membranes and 0.1 nM [^{35}S]-GTPγS in buffer (50 mM HEPES, 0.1 mM NaCl, 10 mM $MgCl_2$, 50 μg/mL saponin, pH 7.5) containing 0.2% fatty acid-free human serum albumin and 5 μM GDP. To test for LPA_1 antagonist activity, the ability of AM095 to inhibit GTPγS binding stimulated by 900 nM LPA (18:1) is measured. Alternatively, to test for agonist effects, the ability of AM095 to stimulate GTPγS binding in the absence of LPA is measured. Reactions are incubated for 30 min at 30°C, before harvesting membranes onto glass filter binding plates (UniFilter GF/B) and washing three times with cold buffer containing 50 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$ using a Brandel 96-tip cell harvester. Plates are dried and then cpm are evaluated by using a Packard TopCount NXT microplate scintillation counter[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	Rats[1] Male Sprague-Dawley rats with surgically implanted jugular vein catheters (250-300 g) are used. In all studies, animals are fasted 15 to 24 h before dosing. For rats, AM095 is administered intraveneously at a dose of 2 mg/kg in 0.9% saline given as a 1 mL/kg bolus injection into the jugular vein. To determine oral exposure, AM095 is administered as a solution in 0.5% methylcellulose via an oral gavage at a dose of 10 mg/kg in a volume of 3 mL/kg. Blood samples (approximately 300 μL of total blood) are taken from each rat via the jugular vein catheter at times up to 24 h postdose (10-11 samples per animal) in potassium EDTA tubes. After each sampling, the catheter is flushed with an equivalent volume of saline. Plasma samples, prepared by centrifugation of whole blood, are stored frozen (−80°C) before analysis. AM095 is dosed intravenously at 2 mg/kg and orally at 5 mg/kg to male beagle dogs (n=3). Plasma samples are collected and analyzed for AM095 concentration by liquid chromatography/mass spectrometry. Mice[2] C57Bl/6 mice are administered the selective LPA_1 antagonist AM095 by oral gavage (30 mg/kg) at time 0 and 8 h, and blood is collected by cardiac puncture under anesthesia in sodium EDTA tubes at 0, 4, 8, 9, 12 and 24 h. Plasma samples are stored at −40°C prior to analysis of AM095 concentrations by liquid chromatography/mass spectrometry (LC-MS/MS). Known amounts of AM095 are added to thawed mouse plasma to yield a concentration range from 0.8 to 4,000 ng/mL. Plasma samples are precipitated using acetonitrile containing the internal standard buspirone. The analyte mixture (10 μL) is injected using a Leap PAL autosampler. Calibration curves are constructed by plotting the peak-area ratio of analyzed peaks against known concentrations. The lower limit of quantitation is 1 ng/mL. The data are subjected to linear regression analysis with $1/x^2$ weighting. The pharmacokinetic parameters of AM095 are calculated by non-compartmental analysis using WinNonlin Professional. C_{max} and time to C_{max} (T_{max}) are obtained directly from the measured data. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- EBioMedicine. 2020 Feb;52:102652.
- Cell Commun Signal. 2023 Sep 25;21(1):257.
- Mol Metab. 2023 Mar 26;101713.
- Mol Pharm. 2023 Oct 16.
- Biomol Ther (Seoul). 2017 Mar 1;25(2):194-201.

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REFERENCES

[1]. Swaney JS, et al. Pharmacokinetic and pharmacodynamic characterization of an oral lysophosphatidic acid type 1 receptor-selective antagonist. J Pharmacol Exp Ther. 2011 Mar;336(3):693-700.

[2]. Castelino FV, et al. Amelioration of dermal fibrosis by genetic deletion or pharmacologic antagonism of lysophosphatidic acid receptor 1 in a mouse model of scleroderma. Arthritis Rheum. 2011 May;63(5):1405-15.

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