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产品名称: 4'-[3-甲基-4-[[[(1R)-1-苯基乙氧基]羰基]氨基]-5-异恶唑基]联苯-4-乙酸钠盐
产品别名: AM095

生物活性:				
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] .			
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] .			
Solvent&Solubility	In Vitro: DMSO : ≥ 170 mg/mL (355.30 mM) * "≥" means soluble, but saturation unknown.			
	Preparing Stock Solutions	Solvent Mass Concentration	1 mg	5 mg
		1 mM	2.0900 mL	10.4500 mL
		5 mM	0.4180 mL	2.0900 mL
		10 mM	0.2090 mL	1.0450 mL
	*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液; 一旦配成溶液, 请分装保存, 避免反复冻融造成的产品失效。 储备液的保存方式和期限: -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。			
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			



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	lysophosphatidic acid receptor 1 in a mouse model of scleroderma. Arthritis Rheum. 2011 May;63(5):1405-15.
实验参考:	
Animal Administration	<p>Rats^[1]</p> <p>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 intravenously 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.</p> <p>Mice^[2]</p> <p>C57Bl/6 mice are administered the selective LPA₁ 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.</p>
Kinase Assay	<p>Known amounts of AM095 (diluted in DMSO) or vehicle (DMSO) are added to 25 to 40 μg of hLPA₁/CHO or mLPA₁/CHO membranes and 0.1 nM [^{35}S]-GTPγS in buffer (50 mM HEPES, 0.1 mM NaCl, 10 mM MgCl₂, 50 μg/mL saponin, pH 7.5) containing 0.2% fatty acid-free human serum albumin and 5 μM GDP. To test for LPA₁ 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 MgCl₂ 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].</p>
References	<p>[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.</p>



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