



上海源叶生物科技有限公司
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产品名称: **MK-0974**
产品别名: **Telcagepant**

生物活性:				
Description	Telcagepant (MK-0974) is a calcitonin gene-related peptide (CGRP) receptor antagonist with K_i of 0.77 nM and 1.2 nM for human and rhesus CGRP receptors, respectively.			
IC ₅₀ & Target	K_i : 0.77 nM (human CGRP), 1.2 nM (rhesus CGRP)			
In Vitro	Telcagepant (MK-0974) displays affinity (K_i) for the canine and rat receptors, with values of 1204 nM and 1192 nM (n=10), respectively. Telcagepant (MK-0974) potently blocks human α -CGRP-stimulated cAMP responses in human CGRP receptor expressing HEK293 cells with an IC ₅₀ of 2.2 nM[1]. Telcagepant (MK-0974) displays saturable binding to SK-N-MC membranes with a K_D of 1.9 nM and B_{max} of 479 fmol/mg protein. Telcagepant (MK-0974) also displays saturable binding to rhesus cerebellum homogenate with a K_D of 1.3 nM and B_{max} of 20 fmol/mg[2].			
In Vivo	Telcagepant (MK-0974) (i.v. bolus, 1 mg/kg) demonstrates that the efficacy of this antagonist is time-dependent and correlated with plasma levels[1]. The pharmacokinetics of Telcagepant (MK-0974) remains linear across 0.5-10 mg/kg intravenous dose in monkeys, but the oral area under the plasma concentration-time curve (AUC) increase (5-30 mg/kg) is 15-fold over dose-proportional[3].			
Solvent&Solubility	In Vitro: DMSO : ≥ 50 mg/mL (88.26 mM) <small>* ">" means soluble, but saturation unknown.</small>			
		<div><div>Solvent</div><div>Mass</div><div>Concentration</div></div>	1 mg	5 mg
	Preparing	1 mM	1.7652 mL	8.8258 mL
	Stock Solutions	5 mM	0.3530 mL	1.7652 mL
		10 mM	0.1765 mL	0.8826 mL
<p>*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。</p> <p>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。</p> <p>In Vivo:</p> <p>请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: ≥ 3 mg/mL (5.30 mM); Clear solution</p> <p>此方案可获得 ≥ 3 mg/mL (5.30 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 μL 30.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀。向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。</p>				



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	<p>2.请依序添加每种溶剂: 10% DMSO→ 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 3 mg/mL (5.30 mM); Clear solution</p> <p>此方案可获得 ≥ 3 mg/mL (5.30 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 30.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水溶液中, 混合均匀。</p> <p>3.请依序添加每种溶剂: 10% DMSO →90% corn oil</p> <p>Solubility: ≥ 3 mg/mL (5.30 mM); Clear solution</p> <p>此方案可获得 ≥ 3 mg/mL (5.30 mM, 饱和度未知) 的澄清溶液, 此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例, 取 100 μL 30.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。</p>
References	<p>[1]. Salvatore CA, et al. Pharmacological characterization of MK-0974 [N-[(3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide], a potent and orally active calcitonin gene-related peptide receptor antagonist for the treatment of migraine. J Pharmacol Exp Ther. 2008 Feb;324(2):416-21. Epub 2007 Nov 26.</p> <p>[2]. Moore EL, et al. Examining the binding properties of MK-0974: a CGRP receptor antagonist for the acute treatment of migraine. Eur J Pharmacol. 2009 Jan 14;602(2-3):250-4.</p> <p>[3]. Roller S, et al. Preclinical pharmacokinetics of MK-0974, an orally active calcitonin-gene related peptide (CGRP)-receptor antagonist, mechanism of dose dependency and species differences. Xenobiotica. 2009 Jan;39(1):33-45.</p>
实验参考:	
Cell Assay	<p>HEK293 cells stably transfected with CLR/RAMP1 are plated in complete growth medium at 85,000 cells/well in 96-well poly-D-lysine-coated plates and cultured for 19 h before assay. Cells are washed with PBS and then incubated with inhibitor in the presence or absence of 50% human serum for 30 min at 37°C and 95% humidity in Cellgro Complete Serum-Free/Low-Protein medium with L-glutamine and 1 g/L bovine serum albumin. Isobutylmethylxanthine is added to the cells at a concentration of 300 μM and incubated for 30 min at 37°C. Human α-CGRP is added to the cells at a concentration of 0.3 nM and allowed to incubate at 37°C for 5 min. After α-CGRP stimulation, the cells are washed with PBS and processed for cAMP determination using the two-stage assay procedure according to the manufacturer's recommended protocol. Dose-response curves are plotted, and IC₅₀ values are determined. [1]</p>
Animal Administration	<p>Monkeys: Rhesus monkeys (male and female) weighing between 4 and 10 kg are anesthetized initially with ketamine (0.1 mL/kg i.m.) and then placed in the supine position on a temperature-controlled water circulating blanket and intubated with a 3-mm tracheal tube connected to 1-liter oxygen/1 to 2% isoflurane gas anesthesia. The right saphenous vein is cannulated for intravenous drug delivery, and blood samples are obtained from the left saphenous artery. Four rubber O-rings (8 mm inner diameter) are placed on the ventral side of the forearm without directly being positioned over a visible vessel. [1]</p>
	<p>[1]. Salvatore CA, et al. Pharmacological characterization of MK-0974</p>



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