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产品名称：Olcegepant
产品别名：BIBN-4096; BIBN 4096BS

生物活性：

Description	Olcegepant is a potent and selective non-peptide antagonist of the calcitonin gene-related peptide 1 (CGRP1) receptor with IC_{50} of 0.03 nM and K_i of 14.4 pM for human CGRP.
IC_{50} & Target	IC50: 0.03 nM (CGRP1)[1] Ki: 14.4 pM (hCGRP)[2]
In Vitro	Olcegepant possesses higher affinity for the human CGRP receptor than the endogenous ligand CGRP and 150-fold higher affinity compared to the peptidic antagonist CGRP8-37. Olcegepant reverses CGRP-mediated vasodilation in human cerebral vessels and inhibits neurogenic vasodilation in a surrogate animal model of migraine pathophysiology[1]. Olcegepant (BIBN4096BS) is extremely potent at primate CGRP receptors exhibiting an affinity (K_i) for human CGRP receptors of 14.4±6.3 (n=4) pM[2]. Several lines of evidence suggest that a calcitonin-gene related peptide (CGRP) receptor antagonist may serve as a novel abortive migraine treatment. Olcegepant (BIBN4096BS) exhibits competitive antagonism at the CGRP receptor present in SK-N-MC cells. Isolated human cerebral, coronary, and omental arteries are studied with a sensitive myograph technique. CGRP induces a concentration-dependent relaxation that is antagonized by Olcegepant in a competitive manner[3].
In Vivo	Olcegepant (BIBN4096BS) in doses between 1 and 30 μg/kg (i.v.) inhibits the effects of CGRP, released by stimulation of the trigeminal ganglion, on facial blood flow in marmoset monkeys[2]. Pre-treatment with Olcegepant (900 μg/kg) inhibits the capsaicin-induced expression of Fos throughout the spinal trigeminal nucleus by 57%. In contrast, the expression of phosphorylated extracellular signal-regulated kinase in the trigeminal ganglion is not changed by Olcegepant pre-treatment[4]. Olcegepant (0.3 to 0.9 mg/kg, i.v.) markedly reduces mechanical allodynia in CCI-ION rats. Olcegepant (0.6 mg/kg, i.v.) significantly reduces the number of c-Fos immunolabeled cells in spinal nucleus of the trigeminal nerve and upregulation of ATF3 transcript (a marker of neuron injury) but not that of interleukin-6 in trigeminal ganglion of CCI-ION rats[5].

In Vitro:

DMSO : ≥ 50 mg/mL (57.49 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.1499 mL	5.7494 mL	11.4989 mL
5 mM	0.2300 mL	1.1499 mL	2.2998 mL
10 mM	0.1150 mL	0.5749 mL	1.1499 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。

In Vivo:

Solvent&Solubility	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： ——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 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (2.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (2.87 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (2.87 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (2.87 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。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Rudolf K, et al. Development of human calcitonin gene-related peptide (CGRP) receptor antagonists. 1. Potent and selective small molecule CGRP antagonists. 1-[N2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-l-lysyl]-4-(4-pyridinyl)piperazine: the first CGRP antagonist for clinical trials in acute migraine. J Med Chem. 2005 Sep 22;48(19):5921-31. [2]. Doods H, et al. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol. 2000 Feb;129(3):420-3. [3]. Edvinsson L, et al. Effect of the CGRP receptor antagonist BIBN4096BS in human cerebral, coronary and omentalarteries and in SK-N-MC cells. Eur J Pharmacol. 2002 Jan 2;434(1-2):49-53. [4]. Sixt ML, et al. Calcitonin gene-related peptide receptor antagonist Olcegepant acts in the spinal trigeminal nucleus. Brain. 2009 Nov;132(Pt 11):3134-41. [5]. Michot B, et al. Differential effects of calcitonin gene-related peptide receptor blockade by Olcegepant on mechanical allodynia induced by ligation of the infraorbital nerve vs the sciatic nerve in the rat. Pain. 2012 Sep;153(9):1939-48.

实验参考：

Cell Assay	Cells are washed with phosphate-buffered saline then pre-incubated with 300 μM isobutylmethylxanthine in serum-free MEM for 30 min at 37 °C α-CGRP-(S-37) or Olcegepant (BIBN4096BS) is added and the cells are incubated for 10 min before the addition of CGRP. The incubation is continued for another 15 min, then the cells are washed with PBS and processed for cAMP determination. Maximal stimulation over basal is defined by using 100 nM CGRP. Dose–response curves are generated by using Prism[3].
	Rats are treated acutely with Olcegepant (0.3, 0.6, and 0.9 mg/kg, intravenously [i.v.] in a tail vein), Naratriptan (0.1 and 0.3 mg/kg subcutaneously [s.c.]), or their respective vehicle. For combined treatment, Olcegepant (0.3 mg/kg, i.v.) is administered 30 minutes before Naratriptan (0.1 mg/kg,

Animal Administration	s.c.). The doses and routes of administration are based on previous reports. For subchronic treatment, CCI-ION and sham-operated rats are injected twice per day for 4 days (at 10 am and 6 pm) with Olcegepant (0.6 mg/kg, i.v.) or its vehicle, starting on the 15th day after ligature. A further injection of Olcegepant (0.6 mg/kg, i.v.) or vehicle is performed at 10 am the subsequent day (19th day after ligature), just before von Frey filament testing.
Kinase Assay	^{125}I-hCGRP is used as the radioligand. The incubation buffer contained (in mM): Tris 50, NaCl 150, $MgCl_2$5 and EDTA 1, (ethylene diamine tetra-acetic acid) pH 7.4. Membrane homogenates are incubated for 180 min at room temperature with 50 pM ^{125}I -hCGRP and increasing concentrations of Olcegepant (BIBN4096BS). The incubation is terminated by filtration through GF/B glass fibre filters using a cell harvester. The protein-bound radioactivity is determined in a gamma counter. The nonspecific binding is defined as radioactivity bound in the presence of 1 μM CGRP. The **IC_{50}** values are obtained by non-linear regression analysis on the basis of a one binding site model [2].
References	[1]. Rudolf K, et al. Development of human calcitonin gene-related peptide (CGRP) receptor antagonists. 1. Potent and selective small molecule CGRP antagonists. 1-[N2-[3,5-dibromo-N-[[4-(3,4-dihydro-2(1H)-oxoquinazolin-3-yl)-1-piperidinyl]carbonyl]-D-tyrosyl]-l-lysyl]-4-(4-pyridinyl)piperazine: the first CGRP antagonist for clinical trials in acute migraine. J Med Chem. 2005 Sep 22;48(19):5921-31. [2]. Doods H, et al. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol. 2000 Feb;129(3):420-3. [3]. Edvinsson L, et al. Effect of the CGRP receptor antagonist BIBN4096BS in human cerebral, coronary and omentalarteries and in SK-N-MC cells. Eur J Pharmacol. 2002 Jan 2;434(1-2):49-53. [4]. Sixt ML, et al. Calcitonin gene-related peptide receptor antagonist Olcegepant acts in the spinal trigeminal nucleus. Brain. 2009 Nov;132(Pt 11):3134-41. [5]. Michot B, et al. Differential effects of calcitonin gene-related peptide receptor blockade by Olcegepant on mechanical allodynia induced by ligation of the infraorbital nerve vs the sciatic nerve in the rat. Pain. 2012 Sep;153(9):1939-48.