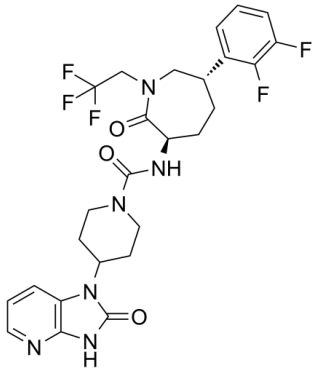
Data Sheet

Product Name:	Telcagepant
Cat. No.:	CS-0291
CAS No.:	781649-09-0
Molecular Formula:	C26H27F5N6O3
Molecular Weight:	566.52
Target:	CGRP Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	DMSO : ≥ 50 mg/mL (88.26 mM)



BIOLOGICAL ACTIVITY:

Telcagepant (MK-0974) is a **calcitonin gene-related peptide (CGRP) receptor** antagonist with **K_i**s of 0.77 nM and 1.2 nM for human and rhesus CGRP receptors, respectively. IC50 & Target: Ki: 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]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 IC_{50} values are determined. **Animal Administration:** [1]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.

References:

[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.

[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.

[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.

CAIndexNames:

1-Piperidinecarboxamide, N-[(3R,6S)-6-(2,3-difluorophenyl)hexahydro-2-oxo-1-(2,2,2-trifluoroethyl)-1H-azepin-3-yl]-4-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]pyridin-1-yl)-

SMILES:

O=C1NC2=C(N1C3CCN(C(N[C@@H]4CC[C@@H](C5=CC=CC(F)=C5F)CN(CC(F)(F)F)C4=O)=O)CC3)C=CC=N2

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