

Product Data Sheet

Product Name: BMS-927711

Cat. No.: GC13705

Chemical Properties

Cas. No. 1289023-67-1

Chemical Name 5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate

SMILES FC1=CC=CC(C2C(N)C(C=CC=N3)=C3C(OC(N4CCC(N5C6=C(N=CC=C6)NC5=O)CC4)=O)CC2)=C1F

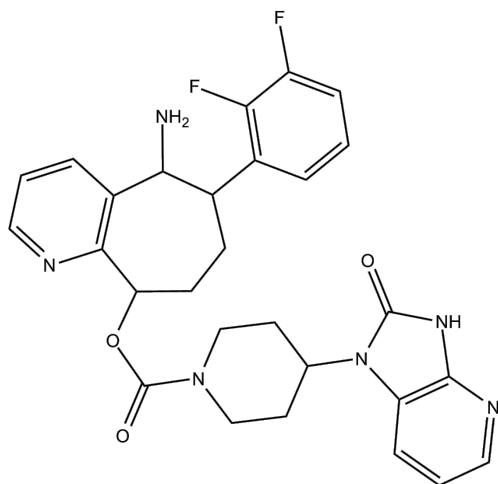
Formula $C_{28}H_{28}F_2N_6O_3$ M.Wt 534.56

Solubility DMF: 5 mg/ml, DMSO: 20 mg/ml, DMSO:PBS (pH 7.2) (1:4): 0.20 mg/ml
Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

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**Animal
experiment:**

Rats[2] Rats are treated with drug-free vehicle (control) or Rimegepant (BMS-927711) in vehicle at 60, 100, and 300 mg/kg once daily via oral gavage. There are 6 rats in each treatment group. For each treatment group, blood is collected at 1, 6, and 24 h from first three rats, and at 3 and 8 h from the second three rats on Day 1 and Day 14 from the tail vein following daily oral dosing of Rimegepant (BMS-927711) for two weeks. The mean hematocrits in the blood are $50.2 \pm 1.8\%$, $49.8 \pm 2.2\%$, $46.4 \pm 5.2\%$ corresponding to the animal groups of 60, 100, and 300 mg/kg doses, respectively. For DBS evaluation, four 15 μ L blood samples are spotted onto DBS cards (4 spots per card), dried at room temperature for at least 2 h, and each card is packaged separately in a ziplock bag with desiccant prior to shipment. The remaining blood in each sample tube is processed to plasma within 1 h of collection and stored at -70°C until analysis. Plasma samples are shipped on dry ice, and DBS cards are shipped at ambient temperature. Rimegepant (BMS-927711) concentrations in rat plasma are analyzed. Rimegepant in rat DBS is analyzed using the DBS method. The toxicokinetic (TK) parameters are calculated from blood concentration and time data using non-compartmental methods using Kinetica.

References:

- [1]. Luo G, et al. Discovery of (5S,6S,9R)-5-amino-6-(2,3-difluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (BMS-927711): an oral calcitonin gene-related peptide (CGRP) antagonist in clinical trials for treating migraine. J Med Chem. 2012 Dec 13;55(23):10644-51.
- [2]. Zheng N, et al. Improved liquid-liquid extraction with inter-well volume replacement dilution workflow and its application to quantify BMS-927711 in rat dried blood spots by UHPLC-MS/MS. J Pharm Biomed Anal. 2014 Feb;89:240-50.

Background

BMS-927711 is an orally potent CGRP receptor antagonist with IC_{50} of 0.14 nM. [1] Calcitonin gene-related peptide CGRP is a 37 amino acid peptide widely distributed in the nervous system, which is a highly potent vasodilator that has been directly implicated in the pathology of

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migraine. Studies have revealed that plasma concentrations of CGRP are elevated during migraine attacks, and these levels could be normalized by sumatriptan in connection with the relief of headache. CGRP receptors are G-coupled cell surface receptors composed of the calcitonin receptor-like receptor (CLR), receptor activity modifying protein 1 (RAMP1), and the receptor component protein (RCP). BMS-927711 is an antagonist of CGRP receptor and could alleviate migraine. [1, 2]

Binding affinities for the human CGRP receptor were determined by inhibition of ¹²⁵I-CGRP binding to SK-N-MC cell membranes, which endogenously express receptor. BMS-927711 was shown to be a full, competitive antagonist with IC₅₀ = 0.14±0.01 nM. Moreover, it showed excellent permeability in tests of PAMPA. Functional receptor antagonism for BMS-927711 was determined by measuring inhibition of CGRP-stimulated cAMP production in SK-N-MC cells. [1]

In a large Phase 2b study testing BMS-927711 for the acute treatment of migraine, an adaptive design to test six doses of BMS-927711 (10, 25, 75, 150, 300 and 600 mg) against placebo was adopted while Sumatriptan 100 mg was used as an active comparator. BMS-927711 was proved to be effective at multiple doses. For the primary endpoint, namely the proportion pain-free at 2 hours post dose, doses of 75 mg, 150 mg and 300 mg (as well as sumatriptan) were superior to placebo. However, 600mg showed no additional benefits over lower doses. Besides, efficacy was numerically inferior to sumatriptan for this endpoint for all doses. [2]

References:

[1]. Luo G, Chen L, Conway C M, et al. Discovery of (5 S, 6 S, 9 R)-5-Amino-6-(2, 3-difluorophenyl)-6, 7, 8, 9-tetrahydro-5 H-cyclohepta [b] pyridin-9-yl 4-(2-oxo-2, 3-dihydro-1 H-imidazo [4, 5-b] pyridin-1-yl) piperidine-1-carboxylate (BMS-927711): An Oral Calcitonin Gene-Related Peptide (CGRP) Antagonist in Clinical Trials for Treating Migraine[J]. *Journal of medicinal chemistry*, 2012, 55(23): 10644-10651.

[2]. Bigal M E. BMS-927711 for the acute treatment of migraine[J]. *Cephalalgia*, 2013: 0333102413500728.

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