

Product Data Sheet

Product Name: Pexacerfont (BMS-562086)

Cat. No.: GC33712

Chemical Properties

Cas. No. 459856-18-9

SMILES CC[C@H](NC1=NC(C)=NC2=C(C3=CC=C(OC)N=C3C)C(C)=NN21)C

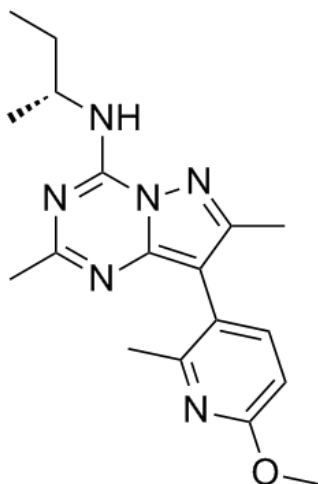
Formula $C_{18}H_{24}N_6O$ M.Wt 340.42

Solubility DMSO: 100 mg/mL (293.75 mM) 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

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

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Cell experiment: Caco-2 cells at passage 50 to 60 are seeded on polycarbonate membranes of 24 well Transwell plates at a density of 60,000 cells/cm². The cells are cultured for 21 to 25 days in culture medium consisting of Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 0.5 mM HEPES, 1% nonessential amino acids, 1% L-glutamine, 100 U/mL penicillin-G, and 100 µg/mL streptomycin. Before the permeability studies, apical (AP) and basolateral (BL) media are replaced with transport buffer (Hanks' balanced salt solution supplemented with 2% N, N-dimethylacetamide, pH 7.4). AP to BL permeability study is initiated by replacing the AP medium with the transport buffer containing 25 µM BMS-562086. All permeability experiments are performed at 37°C. Transepithelial electrical resistance (TEER) values are measured to assess cell monolayer integrity. TEER values are obtained both at the beginning and at the end of each experiment. Only wells with TEER values between 400 and 500 Ω/cm² throughout the experiment are used in the studies. Mannitol (25 or 100 µM) transport experiments are performed in the same manner as other transport experiments. Mannitol served as a probe of the Caco-2 cell monolayer integrity[1].

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Animal experiment: Rats[1] One group of male Sprague-Dawley rats (n=3, 0.34-0.35 kg b.wt.) instrumented with single jugular vein cannulas are designated for oral administration, and a second group of male Sprague-Dawley rats (n=3, 0.34-0.35 kg b.wt.) instrumented with dual jugular vein cannulas are designated for intravenous administration. All rats are fasted for approximately 18 h before use and for 4 h after dosing. Water is provided ad libitum. Pexacerfont (BMS-562086) is administered orally by gavage to three rats at a single dose of 5 mg/kg in 0.5% aqueous methylcellulose. A single intravenous bolus dose of Pexacerfont is administered to three rats at 1 mg/kg in 20% ethanol in saline via the jugular vein cannula. Blood samples (0.2 mL/time point per animal) are collected via the jugular vein cannula for analysis of Pexacerfont at 0, 0.08 (intravenous dose only), 0.17 (intravenous dose only), 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24, 48, 72, and 96 h postdose. Plasma is prepared from the blood samples by centrifuging for 10 min at 1000g and 5°C.

References:

[1]. Zhou L, et al. In vitro and in vivo metabolism and pharmacokinetics of BMS-562086, a potent and orally bioavailable corticotropin-releasing factor-1 receptor antagonist. Drug Metab Dispos. 2012 Jun;40(6):1093-103.

Background

Pexacerfont is a selective corticotropin-releasing factor (CRF1) receptor antagonist with IC₅₀ of 6.1±0.6 nM for human CRF1 receptor.

Pexacerfont demonstrates a potent and specific inhibitory effect (IC₅₀=6.1 ± 0.6 nM) toward human CRF1 receptor and has greater than 1000-fold lower affinity (IC₅₀>1000 nM) for the CRF-binding protein and biogenic amine receptors[1].

Pexacerfont (BMS-562086) is active in rats (1-10 mg/kg, orally) in the defensive withdrawal and elevated plus maze models of anxiety. After the intravenous bolus dose, the plasma Pexacerfont concentrations exhibited a multiexponential decline in rats, dogs, and chimpanzees. The CL_p of Pexacerfont was higher in rats (17.9 mL/kg per min) and dogs (11.6 mL/kg per min) than in

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chimpanzees (2.0 mL/kg per min). Assuming the value of CL_p of Pexacerfont approximates the value of CL_b in these three species, Pexacerfont has an estimated hepatic extraction ratio of 0.32, 0.38, and 0.08 in rats, dogs, and chimpanzees, respectively (calculated by dividing CL_p by respective hepatic blood flow, 55.2, 30.9, and 25.5 mL/kg per min for rats, dogs, and chimpanzees). The assumption that CL_b is equal to CL_p is reasonable at least in rats, where the blood to plasma concentration ratio of BMS-562086-equivalent radioactivity was 0.95 at 1 h postdose[1].

[1]. Zhou L, et al. In vitro and in vivo metabolism and pharmacokinetics of BMS-562086, a potent and orally bioavailable corticotropin-releasing factor-1 receptor antagonist. Drug Metab Dispos. 2012 Jun;40(6):1093-103.

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