

Product Data Sheet

Product Name: BMS 986120

Cat. No.: GC18717

Chemical Properties

Cas. No. 1478712-37-6

Chemical Name 2-methoxy-6-[6-methoxy-4-[[5-methyl-2-(4-morpholinyl)-4-thiazolyl]methoxy]-2-benzofuran-2-yl]-imidazo[2,1-b]-1,3,4-thiadiazole

SMILES COC1=CC2=C(C=C(C3=CN4C(SC(OC)=N4)=N3)O2)C(OCC5=C(C)SC(N6CCOCC6)=N5)=C1

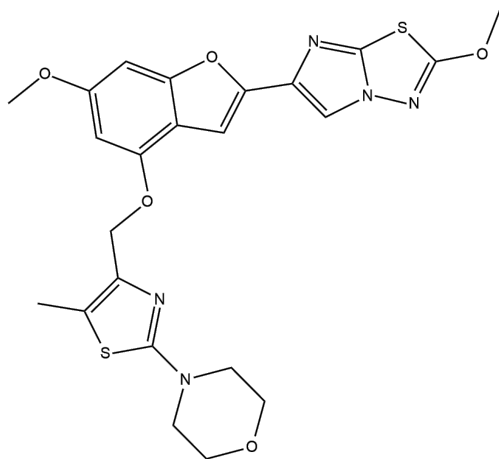
Formula $C_{23}H_{23}N_5O_5S_2$ M.Wt 513.6

Solubility DMSO : 3.33 mg/mL (6.48 mM; ultrasonic and warming and heat to 80°C) 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

Cell experiment [1]:

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Cell lines MEG-01 cells

Preparation Method Cells were stained with calcein-AM (1µg/mL) and pretreated with 10µM of BMS 986120, and then activation peptides selective for protease-activated receptor 1 (PAR1-AP) (100µM), PAR4-AP (100µM), or thrombin (0.1U/mL) were applied for 30 min.

Reaction
Conditions 10µM; 30min

Applications PAR1 and PAR4 activation significantly reduced the circularity of MEG-01 cells, and the reduction in circularity by PAR1 and PAR4 was completely blocked by pretreatment with BMS 986120, respectively.

Animal experiment [2]:

Animal models Monkey

Preparation Method In the BMS 986120 study, 32 monkeys were randomly assigned in a blinded fashion to one of four groups, with eight subjects per group: (i) vehicle, (ii) BMS 986120 (0.2mg/kg), (iii) BMS 986120 (0.5mg/kg), and (iv) BMS 986120 (1mg/kg). On the day of the experiment, monkeys were dosed orally by gavage with BMS 986120 or vehicle [40:60 (w/w) d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)/polyethylene glycol 400 (PEG-400)] at 2ml/kg. Two hours after the last oral dose, blood samples were collected for the measurement of platelet aggregation and concentration of BMS 986120. At the end of the experiment, blood samples were collected for the determination of whole-blood platelet aggregation [agonists: 20µM ADP, collagen (5µg/ml), 18µM PAR1-AP, and 1.56 to 400µM PAR4-AP], clotting times, and plasma concentration of BMS 986120.

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Dosage form 0.2mg/kg; 2h, 4h, 24h; orally by gavage

Applications In blood obtained before oral administration of BMS 986120 (before treatment), all three PAR4-AP concentrations generated maximal aggregation. At 2 and 4 hours after BMS 986120 dosing, the inhibition of platelet aggregation induced by 6.25µM PAR4-AP was near complete, but the aggregation response to 25µM PAR4-AP was unaffected. Consistent with reversible binding to the receptor, the platelet aggregation responses returned to pretreatment baseline by 24 hours in all BMS 986120-treated animals, with drug concentrations dropping below 1nM.

References:

- [1] Heo Y, Jeon H, Namkung W. PAR4-Mediated PI3K/Akt and RhoA/ROCK Signaling Pathways Are Essential for Thrombin-Induced Morphological Changes in MEG-01 Cells. *Int J Mol Sci.* 2022;23(2):776.
- [2] Wong PC, Seiffert D, Bird JE, et al. Blockade of protease-activated receptor-4 (PAR4) provides robust antithrombotic activity with low bleeding. *Sci Transl Med.* 2017;9(371):eaaf5294.

Background

BMS 986120 is a compound specifically targeting protease-activated receptor 4 (PAR4), which comparably inhibited platelet aggregation (PA) induced by activation peptides selective for PAR4 (PAR4-AP) in human and monkey blood in vitro (IC_{50} of 9.5 ± 2.7 and 2.1 ± 0.4 nM, respectively)^[1-2]. BMS 986120 demonstrated excellent antithrombotic efficacy and minimal bleeding time prolongation in monkey models relative to the clinically important antiplatelet agent clopidogrel and provides a potential opportunity to improve the standard of care in the treatment of arterial thrombosis^[3].

In vitro, when MEG-01 cells were pretreated with 10µM BMS 986120 for 30 minutes, the reduction in circularity induced by protease-activated receptor 1 (PAR1) and PAR4 was found to be completely blocked^[4]. The blood was treated with BMS 986120 at concentrations of 0.01, 0.1, and 1µM for 15, 30, and 60 minutes, and BMS 986120 inhibited PAR4-AP-induced platelet activation in a concentration- and time-dependent manner^[5].

In vivo, BMS 986120, administered to Traumatic brain injury (TBI)-injured mice (1mg/kg, 2mg/kg;

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intragastrically), was found to significantly ameliorate the TBI-induced neuronal damage in mice^[6]. In monkeys, administration of BMS 986120 at a dose of 0.2mg/kg via oral gavage resulted in reversible inhibition of platelet aggregation and reduction of thrombus weight, with effects returning to baseline within 24 hours after the last dose^[7].

References:

- [1] Holinstat M, Bray PF. Protease receptor antagonism to target blood platelet therapies. *Clin Pharmacol Ther.* 2016;99(1):72-81.
- [2] Pancras C Wong, et al. Abstract 175: A Novel Orally-Active Small-Molecule Antagonist of the Platelet Protease-Activated Receptor-4, BMS-986120, Inhibits Arterial Thrombosis With Limited Impact on Hemostasis in Cynomolgus Monkeys. *Stroke.* 2018;47:A175.
- [3] Priestley ES, Banville J, Deon D, et al. Discovery of Two Novel Antiplatelet Clinical Candidates (BMS-986120 and BMS-986141) That Antagonize Protease-Activated Receptor 4. *J Med Chem.* 2022;65(13):8843-8854.
- [4] Heo Y, Jeon H, Namkung W. PAR4-Mediated PI3K/Akt and RhoA/ROCK Signaling Pathways Are Essential for Thrombin-Induced Morphological Changes in MEG-01 Cells. *Int J Mol Sci.* 2022;23(2):776.
- [5] Berry J, Harper MT. Protease-activated receptor antagonists prevent thrombosis when dual antiplatelet therapy is insufficient in an occlusive thrombosis microfluidic model. *Res Pract Thromb Haemost.* 2022;6(3):e12703.
- [6] Luo J, Wu X, Liu H, et al. Antagonism of Protease-Activated Receptor 4 Protects Against Traumatic Brain Injury by Suppressing Neuroinflammation via Inhibition of Tab2/NF- κ B Signaling. *Neurosci Bull.* 2021;37(2):242-254.
- [7] Wong PC, Seiffert D, Bird JE, et al. Blockade of protease-activated receptor-4 (PAR4) provides robust antithrombotic activity with low bleeding. *Sci Transl Med.* 2017;9(371):eaaf5294.

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