

Product Data Sheet

Product Name: AM 103
Cat. No.: GC31839

Chemical Properties

Cas. No. 1147872-22-7

SMILES O=C(O)C(C)(C)CC(N1CC2=CC=C(C3=CC=C(OC)N=C3)C=C2)=C(SC(C)(C)C)C4=C1C=CC(OCC5=NC=CC=C5)=C4.[NaH]

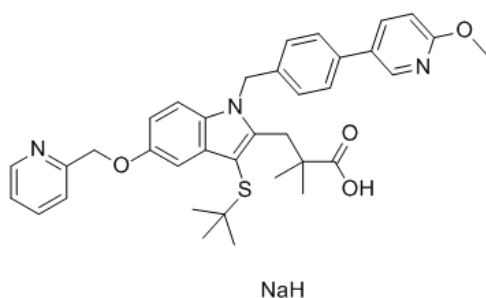
Formula $C_{36}H_{40}N_3NaO_4S$ M.Wt 633.78

Solubility DMSO : 200 mg/mL (316.58 mM; Need ultrasonic) 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.

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**Kinase
experiment:**

Packed human polymorphonuclear cell pellets (1.8×10^9 cells) are resuspended, lysed, and 75,000g membranes. The 75,000g pelleted membranes are resuspended in a Tris buffer (50 mM Tris HCl, pH 7.4, 1 mM EDTA, 1 mM DTT, and 30% glycerol) to yield a protein concentration of appr 4 mg/mL. Then, 2.5 μ g of membrane protein per well is added to 96-well deep well plates containing Tris-Tween buffer (100 mM Tris HCl, pH 7.4, 100 mM NaCl, 1 mM EDTA, 0.5 mM DTT, 5% glycerol, and 0.05% Tween-20) and appr 30,000 cpm of [3H]-3-[5-(pyrid-2-ylmethoxy)-3-tert-butylthio-1-benzyl-indol-2-yl]-2,2-dimethylpropionic acid and test compound in a total volume of 100 μ L and incubated for 60 min at room temperature. The reactions are then harvested onto GF/B filter plates using a Brandel 96-tip harvester and washed 3 $\times$ with 1 mL of ice-cold Tris-Tween buffer. The filter plates are dried, the bottoms sealed, and 100 μ L of scintillant added. The plates are incubated for 1 h before reading on Perkin-Elmer TopCount. Specific binding is defined as total radioactive binding minus nonspecific binding in the presence of 10 μ M MK886. IC₅₀ values are determined using Graphpad prism analysis of drug titration curves.

**Animal
experiment:**

Compounds are administered intravenously (i.v.) (2 mg/kg) to two or three male rats (fasted overnight) as a solution in PEG400/ethanol/water (40/10/50, v/v/v) via a bolus injection into the jugular vein (2 mg/mL; 1 mL/kg) and orally (p.o.) (10 mg/kg) to two or three male rats as a suspension in 0.5% methylcellulose via an oral gavage to the stomach (3.33 mg/mL; 3 mL/kg). Blood samples (approximately 300 μ L) are taken from each rat via the jugular vein cannula at time intervals up to 24 h postdose (8–9 samples per animal). After each sample, the cannula is flushed with an equivalent volume of heparinized saline (0.1 mL at 40 units/mL). Plasma samples, prepared by centrifugation of whole blood, are stored frozen (–80°C) prior to analysis.

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References:

- [1]. Hutchinson JH, et al. 5-lipoxygenase-activating protein inhibitors: development of 3-[3-tert-butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid (AM103). J Med Chem. 2009 Oct 8;52(19):5803-15.
- [2]. Lorrain DS, et al. Pharmacological characterization of 3-[3-tert-butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid (AM103), a novel selective 5-lipoxygenase-activating protein inhibitor that reduces acute and chronic inflammation. J Pharmacol Exp Ther. 2009 Dec;331(3):1042-50.

Background

AM 103 is a potent and selective FLAP inhibitor, with an IC₅₀ value of 4.2 nM.

AM 103 has an IC₅₀ value of 349 nM in the human blood LTB₄ inhibition assay. AM 103 has an excellent CYP profile against the 5 most common CYP isoforms with IC₅₀ values greater than 30 µM for CYP2D6 and >50 µM for CYPs 3A4, 2C9 2C19, and 1A2[1]. AM103 is a novel, potent, and selective FLAP inhibitor with IC₅₀ values of 350, 113, and 117 nM against human, rat, and mouse whole-blood ionophore-stimulated LTB₄ production, respectively[2].

AM 103 has high bioavailability (64%), low clearance (2.9 mL/min/kg), low volume of distribution (0.41 L/kg), and a long i.v. half-life (5.2 h) in dogs. AM 103 (10 mg/kg q.i.d.) inhibits the increase in CysLTs and EPO by approximately 60%, and IL-5 levels are reduced to the concentrations obtained following saline treatment alone in mice[1]. AM103 (1 mg/kg, p.o.) displays >50% inhibition for up to 6 h with a calculated EC₅₀ of appr 60 nM, in a rat ex vivo whole-blood calcium ionophore-induced LTB₄ assay. AM 103 inhibits LTB₄ and cysteinyl leukotriene (CysLT) production with ED₅₀ values of 0.8 and 1 mg/kg, respectively, when rat lung is challenged in vivo with calcium ionophore. In this model, the EC₅₀ derived from plasma AM103 is appr 330 nM for inhibition of both LTB₄ and CysLT. In a model of chronic lung inflammation using ovalbumin-primed and challenged BALB/c mice, AM103 reduces the concentrations of eosinophil peroxidase, CysLTs, and interleukin-5 in the bronchoalveolar lavage fluid. Finally, AM 103 increases survival time in mice exposed to a lethal intravenous injection of platelet-activating factor[2].

- [1]. Hutchinson JH, et al. 5-lipoxygenase-activating protein inhibitors: development of 3-[3-tert-

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butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid (AM103). J Med Chem. 2009 Oct 8;52(19):5803-15. [2]. Lorrain DS, et al. Pharmacological characterization of 3-[3-tert-butylsulfanyl-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-5-(pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid (AM103), a novel selective 5-lipoxygenase-activating protein inhibitor that reduces acute and chronic inflammation. J Pharmacol Exp Ther. 2009 Dec;331(3):1042-50.

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