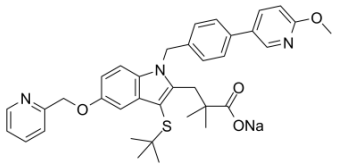
AM103

Cat. No.:	HY-14163
CAS No.:	1147872-22-7
Molecular Formula:	$C_{36}H_{38}N_3NaO_4S$
Molecular Weight:	631.76
Target:	FLAP
Pathway:	Immunology/Inflammation
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	AM 103 is a potent and selective FLAP inhibitor, with an IC_{50} value of 4.2 nM.
IC_{50} & Target	IC50: 4.2 nM (FLAP)[1]
In Vitro	AM 103 has an IC_{50} 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 IC_{50} 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 IC_{50} values of 350, 113, and 117 nM against human, rat, and mouse whole-blood ionophore-stimulated LTB4 production, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	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 EC_{50} 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 ED_{50} values of 0.8 and 1 mg/kg, respectively, when rat lung is challenged in vivo with calcium ionophore. In this model, the EC_{50} 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	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 μg 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 [^{3}H]-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 μL 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× with 1 mL of ice-cold Tris-Tween buffer.

	The filter plates are dried, the bottoms sealed, and 100 μL 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 μM MK886. IC_{50} values are determined using Graphpad prism analysis of drug titration curves. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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 μL) 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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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.

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