

Product Data Sheet

Product Name: PF-543
 Cat. No.: GC11917

Chemical Properties

Cas. No. 1415562-82-1

Chemical Name [(2R)-1-[[4-[[3-(benzenesulfonylmethyl)-5-methylphenoxy]methyl]phenyl]methyl]pyrrolidin-2-yl]methanol

SMILES CC1=CC(=CC(=C1)OCC2=CC=C(C=C2)CN3CCCC3CO)CS(=O)(=O)C4=CC=CC=C4

Formula $C_{27}H_{31}NO_4S$ M.Wt 465.6

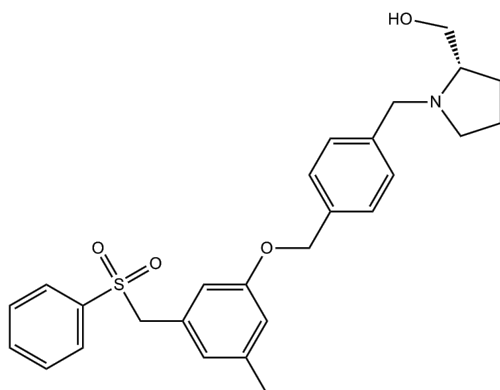
Solubility ≥ 23.3 mg/mL in DMSO, ≥ 51 mg/mL in EtOH with ultrasonic and warming

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]:	
Cell lines	1483 cells

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

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Preparation method	PF-543 modulates the levels of endogenous sphingosine and S1P. Lipids were extracted from 1483 cells treated for 1 h at 37°C in medium lacking serum with a range of concentrations of PF-543(0.01, 0.1, 1, 10, 100, 1000nM). Lipids were quantified using MS
Reaction Conditions	1 μ M ; 1 h
Applications	In 1483 cells pretreated for 1h with a range of concentrations of PF-543, PF-543 dose-dependently depleted the intracellular level of S1P with EC_{50} concentration of 8.4 nM and elevated the intracellular level of sphingosine. PF-543 showed no effect on the growth of several other cancer cell lines. PF-543 inhibited S1P formation in human whole blood (IC_{50} =26.7 nM).
Animal experiment [2]:	
Animal models	Mouse hypoxic model of pulmonary hypertension
Preparation method	Mice were placed into a hypobaric chamber and maintained at 550 mbar atmospheric pressure (~ 10% O ₂ concentration) for a period of 3 weeks. Every second day mice received an intraperitoneal injection of RB-005, PF-543 (10 mg/kg and 1 mg/kg, respectively) or vehicle (20% (2-Hydroxypropyl)- β -cyclodextrin in PBS). The chamber was depressurized and then repressurised in order to inject the mice . Mice were initially dosed (i.p.) with 10 mg/kg or 30 mg/kg of PF-543 for 24 h.
Dosage form	i.p.; 10 mg/kg or 30 mg/kg; 24 h

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Applications	In a mouse hypoxic model of pulmonary hypertension, PF-543 showed no effect on vascular remodelling but reduced right ventricular hypertrophy. Administration of 10 mg/kg PF-543 for 24 h to mice decreased SK1 expression in pulmonary vessels.
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References:

[1] Schnute M E et al. , Modulation of cellular S1P levels with a novel, potent and specific inhibitor of sphingosine kinase-1. Biochem J. 2012, 444(1): 79-88.

[2] MacRitchie N, et al. Effect of the sphingosine kinase 1 selective inhibitor, PF-543 on arterial and cardiac remodelling in a hypoxic model of pulmonary arterial hypertension. Cell Signal. 2016 Aug;28(8):946-55.

Background

PF-543 is a potent, selective, reversible, and sphingosine-competitive inhibitor of SphK1 with an IC_{50} value of 2nM and a K_i value of 3.6 nM^[1]. SphK1 is a kinase that phosphorylates sphingosine to sphingosine-1-phosphate (S1P), which promotes cell growth, survival, and migration, and regulates lymphocyte trafficking. The selectivity of PF-543 for SPHK 1 is over 100 times that of SPHK 2^[2]. PF-543 induces apoptosis, necrosis, and autophagy.

In vitro, PF-543 inhibits the formation of C17-S1P in 1483 cells, with an IC_{50} of 1.0 nM^[1]; PF-543 inhibits SphK1 leading to a dose-dependent depletion of intracellular S1P levels, with an EC_{50} of 8.4 nM and an accompanying increase in intracellular sphingosine levels in 1483 cells^[1]; PF-543 (10-1000 nM; 24h) treatment eliminates SK expression in PASM cells^[1]. Treatment with 200 nM PF-543 for 1h decreased endogenous S1P levels by tenfold in 1483 cells, with a corresponding increase in sphingosine levels^[2]. PF-543 (0.1-10 μ M; 24 h) treatment of PASM cells induces caspase-3/7 activity^[3].

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In vivo, PF-543 (1 mg/kg; intraperitoneal injection; every other day; for 3 weeks) reduces right ventricular hypertrophy in female C57BL/6 J mice, decreases the expression of p53, increases the expression of the antioxidant nuclear factor Nrf-2, but has no effect on vascular remodeling^[3]. When mice were initially treated with an intraperitoneal injection of 10 mg/kg or 30 mg/kg PF-543 for 24 h, the blood sample $T_{1/2}$ was 1.2 h, which could induce a decrease in SK1 expression in the pulmonary vasculature^[3].

References:

[1] Schnute M E et al. , Modulation of cellular S1P levels with a novel, potent and specific inhibitor of sphingosine kinase-1. Biochem J. 2012, 444(1): 79-88.

[2] Hamada M, et al. Induction of autophagy by sphingosine kinase 1 inhibitor PF-543 in head and neck squamous cell carcinoma cells. Cell Death Discov. 2017 Aug 14;3:17047.

[3] MacRitchie N, et al. Effect of the sphingosine kinase 1 selective inhibitor, PF-543 on arterial and cardiac remodelling in a hypoxic model of pulmonary arterial hypertension. Cell Signal. 2016 Aug;28(8):946-55.

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