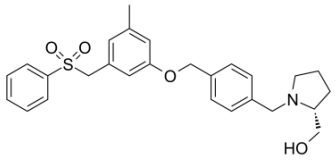
PF-543

Cat. No.:	HY-15425
CAS No.:	1415562-82-1
Molecular Formula:	$C_{27}H_{31}NO_4S$
Molecular Weight:	465.6
Target:	SPHK; LPL Receptor; Apoptosis; Autophagy
Pathway:	Immunology/Inflammation; GPCR/G Protein; Apoptosis; Autophagy
Storage:	Please store the product under the recommended conditions in the COA.



BIOLOGICAL ACTIVITY

Description

PF-543 (Sphingosine Kinase 1 Inhibitor II) is a potent, selective, reversible and sphingosine-competitive **SPHK1** inhibitor with an **IC_{50}** of 2 nM and a **K_i** of 3.6 nM. PF-543 is >100-fold selectivity for **SPHK1** over SPHK2. PF-543 is an effective potent inhibitor of **sphingosine 1-phosphate (S1P)** formation in whole blood with an **IC_{50}** of 26.7 nM. PF-543 induces **apoptosis**, necrosis, and **autophagy**[1][2][3].

IC_{50} & Target

IC50: 2 nM (SPHK1); 26.7 nM (Sphingosine 1-phosphate (S1P))[1]
Ki: 3.6 nM (SPHK1)[1]

In Vitro

PF-543 (10-1000 nM; 24 hours; PASM cells) treatment abolishes SK1 expression at nM concentrations[2].
PF-543 (0.1-10 μM; 24 hours; PASM cells) treatment induces caspase-3/7 activity[2].
PF-543 inhibits C_{17}-S1P formation in 1483 cells with an IC_{50} of 1.0 nM[1].
SphK1 inhibition by PF-543 causes a dose-dependent depletion of the intracellular level of S1P with EC_{50} concentration of 8.4 nM and a concomitant elevation of the intracellular level of sphingosine in 1483 cells. The level of endogenous S1P in 1483 cells after a 1 h treatment with 200 nM PF-543 is decreased 10-fold, producing a proportional increase in the level of sphingosine[1].

Western Blot Analysis[2]

Cell Line:	Human pulmonary arterial smooth muscle (PASM) cells
Concentration:	10 nM, 100 nM, 1000 nM
Incubation Time:	24 hours
Result:	Abolished SK1 expression at nM concentrations.

Apoptosis Analysis[2]

Cell Line:	Human pulmonary arterial smooth muscle (PASM) cells
Concentration:	0.1 μM, 1 μM, 10 μM
Incubation Time:	24 hours
Result:	Induced caspase-3/7 activity in cultured human pulmonary smooth muscle cells.

In Vivo

PF-543 (1 mg/kg; intraperitoneal injection; every second day; for 21 days; female C57BL/6 J mice) treatment has no effect on vascular remodelling but reduces right ventricular hypertrophy. The protection involves a reduction in the expression of p53 and an increase in the expression of anti-oxidant nuclear factor Nrf-2[2].
Mice are initially dosed (ip) with 10 mg/kg or 30 mg/kg of PF-543 for 24 h and the $T_{1/2}$ is 1.2 h in blood samples. Administration of 10 mg/kg PF-543 for 24 h to mice induces a decrease in SK1 expression in pulmonary vessels[2].

Animal Model:	Female C57BL/6 J mice (7-12 week-old) with hypoxic-induced pulmonary arterial hypertension[2]
Dosage:	1 mg/kg
Administration:	Intraperitoneal injection; every second day; for 21 days
Result:	Reduced right ventricular hypertrophy. The protection involves a reduction in the expression of p53 (that promotes cardiomyocyte death) and an increase in the expression of anti-oxidant nuclear factor Nrf-2.

CUSTOMER VALIDATION

- **Mol Cell**. 2020 Mar 19;77(6):1294-1306.e5.
- **Cancer Sci**. 2020 Jul;111(7):2259-2274.
- **Sci Rep**. 2020 Aug 14;10(1):13834.
- **Hum Cell**. 2019 Oct 12.

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REFERENCES

[1]. Schnute ME, et al. Modulation of cellular S1P levels with a novel, potent and specific inhibitor of sphingosine kinase-1. Biochem J. 2012 May 15;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.

[3]. 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.

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