PF-543 hydrochloride

Cat. No.: HY-15425B

CAS No.: 1706522-79-3

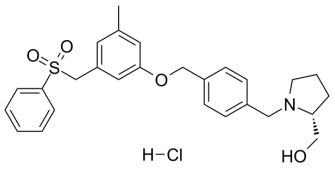
Molecular Formula: $C_{27}H_{32}ClNO_4S$

Molecular Weight: 502.07

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 Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

PF-543 hydrochloride (Sphingosine Kinase 1 Inhibitor II hydrochloride) 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 hydrochloride is >100-fold selectivity for SPHK1 over SPHK2. PF-543 hydrochloride is an effective potent inhibitor of sphingosine 1-phosphate (S1P) formation in whole blood with an IC_{50} of 26.7 nM. PF-543 hydrochloride 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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.
- Sci China Life Sci. 2021 May 27;1-21.
- Cancer Sci. 2020 Jul;111(7):2259-2274.
- Inflammation. 2021 Dec;44(6):2170-2179.
- Sci Rep. 2020 Aug 14;10(1):13834.

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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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