PF-3758309 dihydrochloride

Cat. No.: HY-13007B

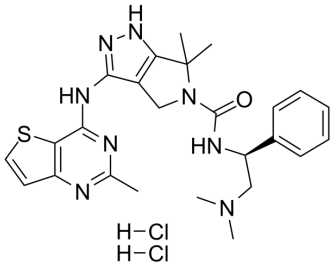
Molecular Formula: $C_{25}H_{32}Cl_2N_8OS$

Molecular Weight: 563.55

Target: PAK; Apoptosis

Pathway: Cell Cycle/DNA Damage; Cytoskeleton; Apoptosis

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

PF-3758309 (PF-03758309) dihydrochloride is a potent, orally available, and reversible ATP-competitive inhibitor of PAK4 (K_d = 2.7 nM; K_i=18.7 nM). PF-3758309 dihydrochloride has the expected cellular functions of a PAK4 inhibitor: inhibition of anchorage-independent growth, induction of apoptosis, cytoskeletal remodeling, and inhibition of proliferation[1][2][3].

IC_{50} & Target

PAK4 18.7 nM (Ki)	PAK1 13.7 nM (Ki)	PAK5 18.1 nM (Ki)	PAK6 17.1 nM (Ki)
PAK2 190 nM (IC_{50})	PAK3 99 nM (IC_{50})	PAK4 2.7 nM (Kd)	

In Vitro

PF-3758309 dihydrochloride has similar enzymatic potency against the kinase domains of the other group B PAKs (PAK5, K_i =18.1 nM; PAK6, K_i=17.1 nM) and group A PAK1 (K_i=13.7 nM), but is less active against the other two group A PAKs (PAK2, IC_{50} =190 nM; PAK3, IC_{50}=99 nM)[1].

In cells, PF-3758309 dihydrochloride inhibits phosphorylation of the PAK4 substrate GEF-H1 (IC_{50}=1.3 nM) and anchorage-independent growth of a panel of tumor cell lines (IC_{50}=4.7 nM)[1].

PF-3758309 dihydrochloride also inhibits endogenous pGEF-H1 accumulation in HCT116 cells. PF-3758309 potently inhibits cellular proliferation (IC_{50}=20 nM) and anchorage-independent growth (IC_{50}=27 nM) of A549 cells[1].

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

In Vivo

PF-3758309 dihydrochloride (7.5-30 mg/kg; p.o.; twice daily for 9-18 days) results in statistically significant tumor growth inhibition (TGI) in HCT116 and A549 models[1].

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

Animal Model:	Female nu/nu, CRL breed 6–8 weeks old mice (bearing HCT116 and A549 tumors)[1]
Dosage:	7.5-30 mg/kg
Administration:	Oral administration; twice daily for 9-18 days
Result:	Significant tumor growth inhibition (TGI) in HCT116 and A549 models.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Exp Cell Res. 2020 Oct 15;395(2):112187.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Murray, Brion W., et al. Small-molecule p21-activated kinase inhibitor PF3758309 is a potent inhibitor of oncogenic signaling and tumor growth. Proceedings of the National Academy of Sciences of the United States of America (2010), 107(20), 9446-9451, S94.

[2]. Zhao ZS, et al. Do PAKs make good drug targets? F1000 Biol Rep. 2010 Sep 23;2:70.

[3]. Ryu BJ, et al. PF-3758309, p21-activated kinase 4 inhibitor, suppresses migration and invasion of A549 human lung cancer cells via regulation of CREB, NF-κB, and β-catenin signalings. Mol Cell Biochem. 2014 Apr;389(1-2):69-77.

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