Product Data Sheet

Product Name: PF 3758309 dihydrochloride
Cat. No.: GC50314

Chemical Properties

Cas. No.			
SMILES	CN(C[C@H](C1=CC=CC=C1)NC(N2CC3=C(C2(C)C)NN=C3NC4=C5SC=CC5=NC(C)=N4)=O)C.Cl.Cl		
Formula	$C_{25}H_{30}N_8OS.2HCl$	M.Wt	563.55
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	PF 3758309 dihydrochloride		

Protocol

Cell experiment [1]:

Cell lines	A549 human lung adenocarcinoma cells; H1299 human lung cancer cells
Preparation Method	A549 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100U/mL penicillin, and 100μg/mL streptomycin at 37°C in a humidified atmosphere of 5% CO_2. A549 cells were treated with PF 3758309 dihydrochloride at various concentrations (0.1–10μM) for 24 hours.
Reaction Conditions	0.1-10μM; 24h

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Applications	PF 3758309 dihydrochloride significantly inhibited the migration and invasion of A549 human lung cancer cells in a dose-dependent manner. PF 3758309 dihydrochloride suppressed the phosphorylation of PAK4 (Ser474), CREB (Ser133), and ERK1/2 (Thr202/Tyr204), and inhibited the transcriptional activities of CREB, NF-κB, and β-catenin pathways. This led to the downregulation of MMP-2 and MMP-9 expressions at both mRNA and protein levels.

Animal experiment [2]:

Animal models	Athymic nude mice bearing human tumor xenografts (HCT116 colorectal carcinoma, A549 lung carcinoma)
Preparation Method	Mice were orally administered PF 3758309 dihydrochloride twice daily (BID) at doses of 7.5-30mg/kg for 9-18 days. Tumor volumes were measured regularly using calipers. For pharmacokinetic/pharmacodynamic (PK/PD) studies, Alzet osmotic minipumps were used to deliver finely controlled drug exposures.
Dosage form	7.5-30mg/kg; oral gavage
Applications	PF 3758309 dihydrochloride significantly inhibited tumor growth in multiple human xenograft models, with >70% tumor growth inhibition (TGI) in sensitive models including HCT116 and A549. The plasma EC_{50} value was determined to be 0.4nM in the most sensitive model. PF 3758309 dihydrochloride was not active in DLD1 cells (loss-of-function PAK4 mutation) or cMet-driven GTL16 model.

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References:
[1] Ryu BJ, Lee H, Kim SH, et al. PF 3758309 dihydrochloride, 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.
[2] Murray BW, Guo C, Piraino J, et al. Small-molecule p21-activated kinase inhibitor PF 3758309 dihydrochloride is a potent inhibitor of oncogenic signaling and tumor growth. Proc Natl Acad Sci U S A. 2010 May 18;107(20):9446-51.

Background

PF 3758309 dihydrochloride is an ATP-competitive p21-activated kinase 4 (PAK4) inhibitor with a Kd value of 2.7nM and a Ki value of 18.7nM[1]. PF 3758309 dihydrochloride can induce apoptosis, cytoskeletal remodeling, and inhibit cell proliferation[2]. PF 3758309 dihydrochloride can suppress the proliferation of cancer cells[3]. PF 3758309 dihydrochloride has the ability to inhibit HIV virus replication[4].

In vitro, pretreatment of patient-derived pancreatic ductal adenocarcinoma cell lines (TKCC-15) with PF 3758309 dihydrochloride (2.5–10μM) for 48 hours significantly inhibited cell proliferation and enhanced chemosensitivity[5]. Pretreatment of A549 human lung cancer cells with PF 3758309 dihydrochloride (0.1–10μM) for 24 hours significantly suppressed cell migration and invasion capabilities, while downregulating the expression of matrix metalloproteinases MMP-2 and MMP-9[6].

In vivo, oral administration of PF 3758309 dihydrochloride (25mg/kg) twice daily to nude mice bearing colorectal cancer cell line xenografts or patient-derived tumor xenografts (PDTX) for 14–56 days significantly inhibited tumor growth and reduced intratumoral drug concentration[7]. Oral administration of PF 3758309 dihydrochloride (7.5–30mg/kg) twice daily to nude mice bearing human tumor xenografts (such as HCT116, A549) for 9–18 days significantly suppressed tumor

growth and induced tumor cell apoptosis[8].

References:
[1] Huynh N, Liu KH, Yim M, et al. Demonstration and biological significance of a gastrin-P21-activated kinase 1 feedback loop in colorectal cancer cells. Physiol Rep. 2014 Jun 24;2(6):e12048.
[2] Ramos-Alvarez I, Jensen RT. P21-activated kinase 4 in pancreatic acinar cells is activated by numerous gastrointestinal hormones/neurotransmitters and growth factors by novel signaling, and its activation stimulates secretory/growth cascades. Am J Physiol Gastrointest Liver Physiol. 2018 Aug 1;315(2):G302-G317.
[3] Dukel M, Fiskin K. Combination of PAKs inhibitors IPA-3 and PF 3758309 dihydrochloride effectively suppresses colon carcinoma cell growth by perturbing DNA damage response. Int J Radiat Biol. 2023;99(2):340-354.
[4] Vargas B, Boslett J, Yates N, et al. Mechanism by Which PF 3758309 dihydrochloride, a Pan Isoform Inhibitor of p21-Activated Kinases, Blocks Reactivation of HIV-1 Latency. Biomolecules. 2023 Jan 4;13(1):100.
[5] Wang K, Huynh N, Wang X, et al. PAK inhibition by PF 3758309 dihydrochloride enhanced the sensitivity of multiple chemotherapeutic reagents in patient-derived pancreatic cancer cell lines. Am J Transl Res. 2019 Jun 15;11(6):3353-3364.
[6] Ryu BJ, Lee H, Kim SH, et al. PF 3758309 dihydrochloride, 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.
[7] Bradshaw-Pierce EL, Pitts TM, Tan AC, et al. Tumor P-Glycoprotein Correlates with Efficacy of PF 3758309 dihydrochloride in in vitro and in vivo Models of Colorectal Cancer. Front Pharmacol. 2013 Mar 22;4:22.
[8] Murray BW, Guo C, Piraino J, et al. Small-molecule p21-activated kinase inhibitor PF 3758309 dihydrochloride is a potent inhibitor of oncogenic signaling and tumor growth. Proc Natl Acad Sci U S A. 2010 May 18;107(20):9446-51.

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