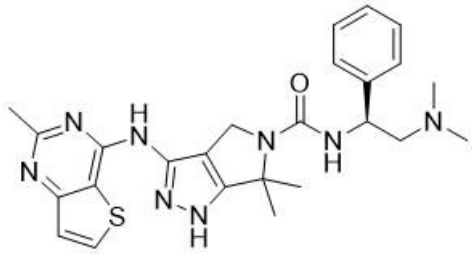
Product data sheet

MedKoo Cat#: 205581 Name: PF-03758309 CAS#: 898044-15-0 (free base) Chemical Formula: $C_{25}H_{30}N_8OS$ Exact Mass: 490.22633 Molecular Weight: 490.62	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

PF-3758309, also known as PF-03758309, is a PAK4 inhibitor, is also a n orally bioavailable small-molecule inhibitor of p21-activated kinase 4 (PAK4) with potential antineoplastic activity. PAK4 inhibitor PF-03758309 binds to PAK4, inhibiting PAK4 activity and cancer cell growth. PAK4, a serine/threonine kinase belonging to the p21-activated kinase (PAK) family, is often upregulated in a variety of cancer cell types and plays an important role in cancer cell motility, proliferation, and survival.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	10.0	20.4

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.04	10.19	20.38
5 mM	0.41	2.04	4.08
10 mM	0.20	1.02	2.04
50 mM	0.04	0.20	0.41

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Wang K, Huynh N, Wang X, Pajic M, Parkin A, Man J, Baldwin GS, Nikfarjam M, He H. PAK inhibition by PF-3758309 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. PMID: 31312349; PMCID: PMC6614655.
2. Li Z, Li X, Xu L, Tao Y, Yang C, Chen X, Fang F, Wu Y, Ding X, Zhao H, Li M, Qian G, Xu Y, Ren J, Du W, Wang J, Lu J, Hu S, Pan J. Inhibition of neuroblastoma proliferation by PF-3758309, a small-molecule inhibitor that targets p21-activated kinase 4. Oncol Rep. 2017 Nov;38(5):2705-2716. doi: 10.3892/or.2017.5989. Epub 2017 Sep 22. PMID: 29048629; PMCID: PMC5780023.

In vivo study

1. Bradshaw-Pierce EL, Pitts TM, Tan AC, McPhillips K, West M, Gustafson DL, Halsey C, Nguyen L, Lee NV, Kan JL, Murray BW, Eckhardt SG. Tumor P-Glycoprotein Correlates with Efficacy of PF-3758309 in in vitro and in vivo Models of Colorectal Cancer. Front Pharmacol. 2013 Mar 22;4:22. doi: 10.3389/fphar.2013.00022. PMID: 23524533; PMCID: PMC3605511.
2. Wang K, Huynh N, Wang X, Baldwin G, Nikfarjam M, He H. Inhibition of p21 activated kinase enhances tumour immune response and sensitizes pancreatic cancer to gemcitabine. Int J Oncol. 2018 Jan;52(1):261-269. doi: 10.3892/ijo.2017.4193. Epub 2017 Nov 7. PMID: 29115428.

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7. Bioactivity

Biological target:

PF-3758309 is a potent, reversible ATP-competitive inhibitor of PAK4 (Kd= 2.7 nM; Ki=18.7 nM) with IC_{50}s of 190nM and 99nM for PAK2 and PAK3, respectively.

In vitro activity

In the present study, using high-throughput small-molecule inhibitor screening, it was attempted to evaluate the antitumor effect and molecular mechanism of PF-3758309 in human neuroblastoma. To evaluate the inhibitory effect of PF-3758309 (Fig. 2D) on neuroblastoma cells, 8 neuroblastoma cell lines were treated with the PAK4 inhibitor PF-3758309 (Fig. 2E). Pharmacological inhibition of PAK4 by PF-3758309 treatment resulted in significant inhibition of proliferation in neuroblastoma cells with high expression of PAK4, that is, KELLY, NBL-S, SH-SY5Y and IMR-32 cells. In contrast, cells with low levels of PAK4 expression were less sensitive to PF-3758309 exposure. PF-3758309 treatment was found to have a dose-dependent inhibitory effect on the growth of neuroblastoma cells (Fig. 2E). The IC50 value of PF-3758309 was determined in 4 neuroblastoma cell lines: SH-SY5Y, 5.461 µM; IMR-32, 2.214 µM; NBL-S, 14.02 µM; KELLY 1.846 µM. The cells that were affected by PF-3758309 presented with abnormal morphological features; most of the cells had shrunk and lost their ability to adhere, and they were observed to be floating (Fig. 2F). In addition, clone formation assay showed that PF-3758309 caused a reduction in the number of both SH-SY5Y and IMR-32 cell clones (Fig. 3A and B). These results demonstrate that PF-3758309 effectively impairs the growth potential of neuroblastoma cells.

Oncol Rep. 2017 Nov; 38(5): 2705–2716. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5780023/

In vivo activity

The effects of p21 activated kinases (PAKs) on tumour immune response and gemcitabine response were examined in PDA. An orthotopic murine PDA model, in which pancreatic cancer cells were injected to the tail of pancreas, was used. The mice were treated with PAK inhibitor, PF-3758309, plus or minus gemcitabine. Tumour growth was measured by volume and weight. In PAK1 WT mice, either PF-3758309 or gemcitabine alone significantly reduced tumour growth by decreasing the tumour volume (Fig. 6A and C) and tumour weight (Fig. 6B), compared to untreated controls. Either PF-3758309 or gemcitabine alone inhibited tumour growth by decreasing cell proliferation as measured by Ki67 immunohistochemistry (Fig. 7A). The proliferation in tumours from PAK1 WT mice treated with either PF-3758309 or gemcitabine was reduced to 60.6% and 60.1% of that in tumours from untreated mice. These results indicate that inhibition of PAKs by PF-3758309 or by PAK1 knockout sensitized pancreatic cancers to gemcitabine in vivo at least by decreasing cell proliferation.

Int J Oncol. 2018 Jan;52(1):261-269. https://pubmed.ncbi.nlm.nih.gov/29115428/