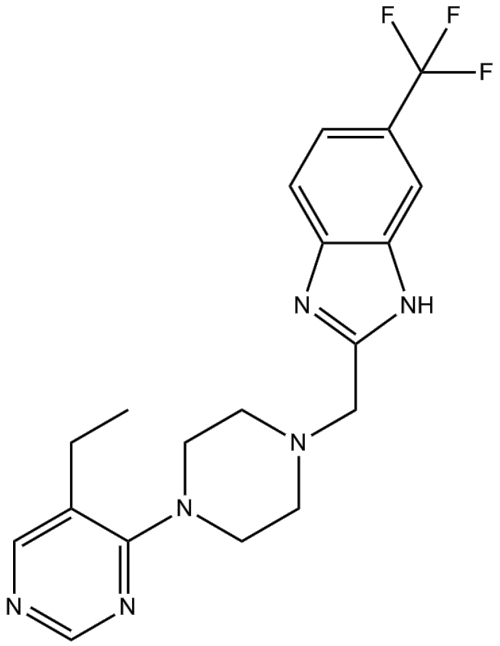
Product Data Sheet

Product Name: PF-4708671
Cat. No.: GC10689

Chemical Properties

Cas. No.	1255517-76-0		
Chemical Name	2-[[4-(5-ethylpyrimidin-4-yl)piperazin-1-yl]methyl]-6-(trifluoromethyl)-1H-benzimidazole		
SMILES	CCC1=CN=CN=C1N2CCN(CC2)CC3=NC4=C(N3)C=C(C=C4)C(F)(F)F		
Formula	C19H21F3N6	M.Wt	390.41
Solubility	≥ 19.5mg/mL in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C 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



Protocol

Cell experiment [1]:

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Cell lines	A549 (adenocarcinoma), NCI-H460 (large cell carcinoma), and SK-MES-1 (squamous cell carcinoma) cells
Preparation Method	Tumor cells were seeded in 96-well plates at a density of 5×103 per well. After incubation in presence of PF-4708671 (0.1μM, 0.3μM, 1μM, 3μM and 10μM) for 24, 48 and 72 hours, respectively,
Reaction Conditions	0.1μM, 0.3μM, 1μM, 3μM and 10μM for 24, 48 and 72 hours
Applications	Proliferation abilities of the three NSCLC cell lines were significantly inhibited by PF-4708671. After 24 hours of treatment, PF-4708671 inhibited H460 cell proliferation at 10μM, and A549 and SK-MES-1 cell amounts were significantly reduced at 3μM and 0.1μM, respectively. In addition, H460, A549, and SK-MES-1 cell growth rates were significantly inhibited by PF-4708671 at 0.3μM, 0.1μM, and 0.1μM, respectively, 48 hours post treatment. All cell lines showed significantly reduced proliferation at 72 hour after treatment with 0.1μM PF-4708671.

Animal experiment [2]:

Animal models	Male C57Bl/6 mice (6 weeks old)
Preparation Method	Mice were randomly assigned to three groups: (1) control (HF) receiving vehicle (8% EtOH [vol./vol.], 0.2% [wt/vol.] carboxymethylcellulose sterile); (2) treated with PF-4708671 (35 mg kg-1 day-1, i.p.); or (3) treated with rapamycin (2 mg kg-1 day-1, i.p.) for 7 days while being kept on the same high-fat diet.
Dosage form	Intraperitoneal injection, 35 mg kg-1 day-1 for 7 days.

Caution: Product has not been fully validated for medical applications. For research use only.
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Applications	PF-4708671 did not affect body weight or adiposity, 1 week of PF-4708671 treatment was found to improve fasting glucose whereas rapamycin further increased fasting hyperglycaemia in obese mice.

References:

[1]: Qiu ZX, Sun RF, Mo XM and Li WM: The p70S6K specific inhibitor PF-4708671 impedes non-small cell lung cancer growth. PLoS One. 11:e01471852016.
[2]: M. Shum, K. Bellmann, P. St-Pierre, A. Marette. Pharmacological inhibition of S6K1 increases glucose metabolism and Akt signalling in vitro and in diet-induced obese mice .Diabetologia, 59 (2016), pp. 592-603

Background

PF-4708671, is a novel cell-permeable inhibitor of S6K1, specifically inhibits the S6K1 isoform with a Ki of 20 nM and IC50 of 160 nM. [1].

PF-4708671 prevents the S6K1-mediated phosphorylation of S6 protein in response to IGF-1 (insulin-like growth factor 1), PF-4708671 was also found to induce phosphorylation of the T-loop and hydrophobic motif of S6K1, an effect that is dependent upon mTORC1 (mTOR complex 1) [1]. RSK1, RSK2 and MSK1 were the other kinases inhibited by PF-4708671 (IC50 = 4.7 μM, 9.2 μM and 0.95 μM, respectively). PF-4708671 decreased phosphorylation of ribosomal protein S6 in HEK-293 cells. PF-4708671 has been used as the standard S6K1 inhibitor for the investigation of the role of S6K1 in several cancers. PF-4708671 in combination with tamoxifen was shown to be highly effective against ER+ MCF7 cells that had overexpression of S6K1 [2] and enhanced cell death in glucose-starved MCF7 cells via downregulation of anti-apoptotic proteins Mcl-1 and survivin [3].

PF-4708671 inhibite the AKT/mTOR/S6K1 pathway led to the inhibition of cell migration in triple-negative MDA-MB-231 cells and inhibition of local relapse in mice models [4]. Moreover, PF-4708671 improved glucose tolerance in high-fat -fed obese mice by restoring Akt S473 phosphorylation in metabolic tissues [5]. PF-4708671 has protective effects against NMDA-induced retinal neurotoxicity in rats [6].

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References:

[1]. Pearce, L. R. et al. Characterization of PF-4708671, a novel and highly specific inhibitor of p70 ribosomal S6 kinase (S6K1). Biochem. J. 431, 245-255 (2010).
[2]. Hong SE, Kim EK, Jin HO, Kim HA, Lee JK, Koh JS, et al. S6K1 inhibition enhances tamoxifen-induced cell death in MCF-7 cells through translational inhibition of Mcl-1 and survivin. Cell Biol Toxicol. 2013;29(4):273-82.
[3]. Choi HN, Jin HO, Kim JH, Hong SE, Kim HA, Kim EK, et al. Inhibition of S6K1 enhances glucose deprivation-induced cell death via downregulation of anti-apoptotic proteins in MCF-7 breast cancer cells. Biochem Biophys Res Commun. 2013;432(1):123-8.
[4]. Segatto I, Berton S, Sonego M, Massarut S, D'Andrea S, Perin T, et al. Inhibition of breast cancer local relapse by targeting p70S6 kinase activity. J Mol Cell Biol. 2013;5(6):428-31.
[5]. M. Shum, K. Bellmann, P. St-Pierre, A. Marette. Pharmacological inhibition of S6K1 increases glucose metabolism and Akt signalling in vitro and in diet-induced obese mice .Diabetologia, 59 (2016), pp. 592-603
[6]. Hayashi, I.; Aoki, Y.; Ushikubo, H.; Asano, D.; Mori, A.; Sakamoto, K.; Nakahara, T.; Ishii, K. Protective effects of PF-4708671 againstN-methyl-d-aspartic acid-induced retinal damage in rats. Fundam. Clin. Pharmacol. 2016, 30, 529-536.

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