

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

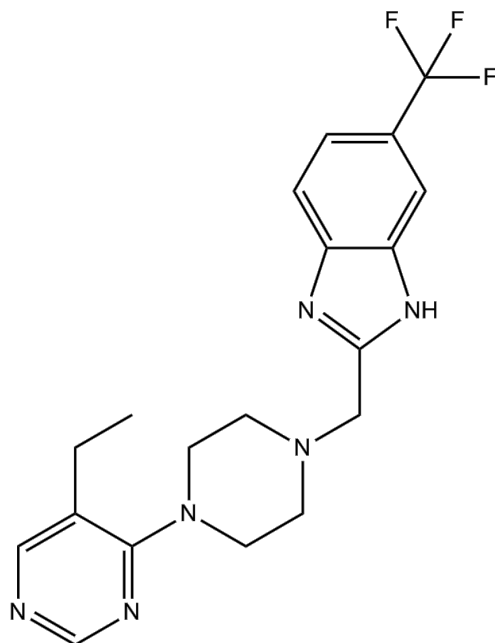
Formula C₁₉H₂₁F₃N₆ M.Wt 390.41

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 5×10^3 per well. After incubation in presence of PF-4708671 (0.1 μ M, 0.3 μ M, 1 μ M, 3 μ M and 10 μ M) for 24, 48 and 72 hours, respectively,

Reaction Conditions 0.1 μ M, 0.3 μ M, 1 μ M, 3 μ M and 10 μ M 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 10 μ M, and A549 and SK-MES-1 cell amounts were significantly reduced at 3 μ M and 0.1 μ M, respectively. In addition, H460, A549, and SK-MES-1 cell growth rates were significantly inhibited by PF-4708671 at 0.3 μ M, 0.1 μ M, and 0.1 μ M, respectively, 48 hours post treatment. All cell lines showed significantly reduced proliferation at 72 hour after treatment with 0.1 μ M 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.

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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 K_i of 20 nM and IC_{50} 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 (IC_{50} = 4.7 μ M, 9.2 μ M and 0.95 μ M, 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, Sonogo 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 against N-methyl-D-aspartic acid-induced retinal damage in rats. *Fundam. Clin. Pharmacol.* 2016, 30, 529-536.

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