PF-4989216

Cat. No.: HY-13864

CAS No.: 1276553-09-3

Molecular Formula: $C_{18}H_{13}FN_6OS$

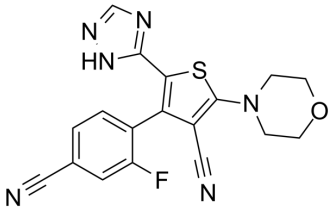
Molecular Weight: 380.4

Target: PI3K; Apoptosis

Pathway: PI3K/Akt/mTOR; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 29 mg/mL (76.24 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6288 mL	13.1441 mL	26.2881 mL
5 mM	0.5258 mL	2.6288 mL	5.2576 mL
10 mM	0.2629 mL	1.3144 mL	2.6288 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.57 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.57 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-4989216 is a potent and selective PI3Kα inhibitor with a K_i of 0.6 nM.

IC_{50} & Target

PI3Kα	mTOR
0.6 nM (Ki)	1440 nM (Ki)

In Vitro

PF-4989216 (Compound 10) has excellent PI3Kα K_i (0.6 nM), good cellular potency (S473 IC_{50}=79 nM), and good selectivity against mTOR (mTOR K_i=1440 nM). PF-4989216 has PI3Kα K_i less than 1 nM and mTOR K_i more than 1 μM. PF-4989216 also has excellent selectivity over 40 other kinases, and no major CYP inhibitions are observed. Less than 30% inhibition is observed in 1A2, 2C9, 2D6, and 3A4 CYP enzymes at 3 μM[1]. The toxicity of PF-4989216 in several drug-sensitive and MDR

	cancer cell lines, including cells overexpressing ABCB1 or ABCG2, and in HEK293 cells transfected with human ABCB1 or ABCG2 is determined. PF-4989216 inhibits human colon carcinoma S1 cell line and ABCG2-overexpressing subline S1-M1-80 with IC_{50}s of 1.11±0.09 and 6.79±1.00 uM, respectively. PF-4989216 inhibits human breast carcinoma MCF-7 and ABCG2-overexpressing sublines MCF7-FLV1000 and MCF7-AdVp3000 IC_{50}s of 2.30±0.68, 23.26±2.94 and 62.57±5.46 uM, respectively. PF-4989216 inhibits pcDNA-HEK293, ABCB1-transected MDR19-HEK293, ABCG2-tranfected R482-HEK293 cells with IC_{50}s of 0.44±0.05, 0.38±0.06 and 5.05±0.89 uM, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PF-4989216 (Compound 10) is dosed orally in our in vivo antitumor model, PI3K driven NCI-H1975 xenograft tumors. PF-4989216 demonstrates dose responsive tumor growth inhibitory activity from 25 to 200 mg/kg in QD oral dosing[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	MTT and CCK-8 assays are performed to determine the general sensitivities of cells to the tested drugs. The human colon carcinoma S1 cell line and ABCG2-overexpressing subline S1-M1-80 are treated with PF-4989216 (0.1, 1 and 10 μM). The human breast carcinoma MCF-7 and ABCG2-overexpressing sublines MCF7-FLV1000 and MCF7-AdVp3000 are treated with PF-4989216 (0.1, 1, 10 and 100 μM).The parental HEK293 and ABCG2-tranfected R482-HEK293 cells are treated with PF-4989216 (0.01, 0.1, 1 and 10 μM). For the reversal of cytotoxicity assays, PF-4989216 or Ko143 or Lapatinib at a nontoxic concentration is added into the cytotoxicity assay, and the extent of reversal is then calculated[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] For animal studies, 6-8 week old nu/nu athymic female mice are used. Tumors are established by injecting 2×10^6 cells suspended 1:1 (v/v) with reconstituted basement membrane. For tumor growth inhibition studies, mice with established tumors of ~150 mm^3 are randomized. PF-4989216 (Compound 10) is dosed orally (25, 50, 100 and 200 mg/kg) in a mouse PI3K driven NCI-H1975 xenograft tumor model. Tumor dimensions are measured with vernier calipers, and tumor volumes are calculated. Tumor growth inhibition percentage (TGI %) is calculated. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Liu KK, et al. Highly Selective and Potent Thiophenes as PI3K Inhibitors with Oral Antitumor Activity. ACS Med Chem Lett. 2011 Sep 19;2(11):809-813.

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