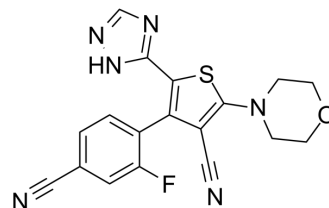


PF-4989216

Cat. No.:	HY-13864		
CAS No.:	1276553-09-3		
Molecular Formula:	C ₁₈ H ₁₃ FN ₆ OS		
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	1 mg	5 mg	10 mg
	Concentration				
	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

- 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
- 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 PI3K α inhibitor with a K_i of 0.6 nM.

IC₅₀ & Target

PI3K α	mTOR
0.6 nM (K _i)	1440 nM (K _i)

In Vitro

PF-4989216 (Compound 10) has excellent PI3K α K_i (0.6 nM), good cellular potency (S473 IC₅₀=79 nM), and good selectivity against mTOR (mTOR K_i=1440 nM). PF-4989216 has PI3K α K_i less than 1 nM and mTOR K_i more than 1 μ M. 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 μ M^[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 IC₅₀s of 1.11±0.09 and 6.79±1.00 μM, respectively. PF-4989216 inhibits human breast carcinoma MCF-7 and ABCG2-overexpressing sublines MCF7-FLV1000 and MCF7-AdVp3000 IC₅₀s of 2.30±0.68, 23.26±2.94 and 62.57±5.46 μM, respectively. PF-4989216 inhibits pcDNA-HEK293, ABCB1-transfected MDR19-HEK293, ABCG2-transfected R482-HEK293 cells with IC₅₀s of 0.44±0.05, 0.38±0.06 and 5.05±0.89 μM, 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-transfected 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 2×10⁶ cells suspended 1:1 (v/v) with reconstituted basement membrane. For tumor growth inhibition studies, mice with established tumors of ~150 mm³ 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.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898

Fax: 609-228-5909

E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA