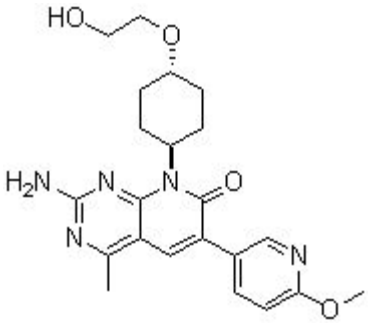
Product Introduction

PF-04691502

PF-04691502 is an ATP-competitive PI3K(α/β/δ/γ)/mTOR dual inhibitor with K_i of 1.8 nM/2.1 nM/1.6 nM/1.9 nM and 16 nM, little activity against either Vps34, AKT, PDK1, p70S6K, MEK, ERK, p38, or JNK. Phase 2.

Technical Data:

Molecular Weight (MW):	425.48	
Formula:	$C_{22}H_{27}N_5O_4$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 14 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃ Powder	
	6 months-80℃ in DMSO	
CAS No.:	1013101-36-4	

Biological Activity

PF-04691502 potently inhibits recombinant class I PI3K and mTOR in biochemical assays and suppresses transformation of avian fibroblasts mediated by wild-type PI3K γ, δ, or mutant PI3Kα. In PIK3CA-mutant and PTEN-deleted cancer cell lines, PF-04691502 reduces phosphorylation of AKT T308 and AKT S473 (IC(50) of 7.5-47 nM and 3.8-20 nM, respectively) and inhibits cell proliferation (IC(50) of 179-313 nM). PF-04691502 inhibits mTORC1 activity in cells as measured by PI3K-independent nutrient stimulated assay, with an IC(50) of 32 nM and inhibits the activation of PI3K and mTOR downstream effectors

including AKT, FKHRL1, PRAS40, p70S6K, 4EBP1, and S6RP. Short-term exposure to PF-04691502 predominantly inhibits PI3K, whereas mTOR inhibition persists for 24 to 48 hours. PF-04691502 induces cell cycle G(1) arrest, concomitant with upregulation of p27 Kip1 and reduction of Rb. [1]

Antitumor activity of PF-04691502 is observed in U87 (PTEN null), SKOV3 (PIK3CA mutation), and gefitinib- and erlotinib-resistant non-small cell lung carcinoma xenografts. [1] PF-04691502 inhibits tumor growth at 7 days by 72%. FDG-PET imaging revealed that PF-04691502 reduces glucose metabolism dramatically. Tissue biomarkers of PI3K/mTOR pathway activity, p-AKT (S473), and p-RPS6 (S240/244), are also dramatically inhibited following PF-04691502 treatment. [2]

References

[1] Yuan J, Mol Cancer Ther, 2011, 10(11), 2189-2199

[2] Kinross KM, Mol Cancer Ther, 2011, 10(8), 1440-1449

[3] Simmons BH, Cancer Chemother Pharmacol, 2012, 70(2), 213-220

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