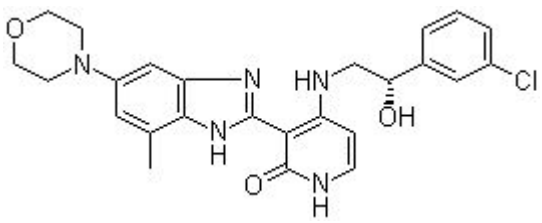
Product Introduction

BMS-536924

BMS-536924 is an ATP-competitive **IGF-1R/IR** inhibitor with **IC50** of 100 nM/73 nM, modest activity for Mek, Fak, and Lck with very little activity for Akt1, MAPK1/2.

Technical Data:

Molecular Weight (MW):	479.96	
Formula:	$C_{25}H_{26}ClN_5O_3$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 96 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	468740-43-4	

Biological Activity

BMS-536924 also inhibits FAK and Lck with IC50 of 150 nM and 341 nM, respectively. BMS-536924 inhibits cellular proliferation and disrupts Akt and MAPK phosphorylation. [1] BMS-536924 inhibits IGF-I-stimulated IGF-1R signaling in MCF10A cells and blocks constitutive IGF-1R activity in CD8-IGF-1R-MCF10A. Preincubation of MCF10A cells with 1 μM BMS-536924 completely blocks the ability of IGF-I to stimulate IGF-1R phosphorylation. IGF-I stimulation results in increased phosphorylation of ERK1/2, GSK3β, and Akt.

BMS-536924 inhibits this ligand-induced phosphorylation. Treatment of the CD8-IGF-1R-MCF10A cells with BMS-536924 results in a dose-dependent inhibition of phosphorylation with partial inhibition at 0.01 μM and 0.1 μM, but complete receptor inhibition at a concentration of 1 μM. Maximal inhibition of phosphorylated IGF-1R is observed as early as 10 minutes following incubation. BMS-536924 retains its ability to inhibit IGF-1R phosphorylation for up to 48 hours. Addition of BMS-536924 time-dependently inhibits Akt phosphorylation starting at 1 hour. By 48 hours, Akt activation is completely blocked. [2] Treatment with BMS-536924 shows antiproliferation activity in a panel of cancer cell lines including TC32, HT1080/S, SK-LMS-1, H513 and CTR cells. pIGF-1R/pIR is activated upon IGF-I/insulin stimulation and the activation is inhibited by BMS-536924 at similar potencies in Rh41 and Rh36 cell lines. The expression of programmed cell death 4 (PDCD4), cleavage of poly(ADP-ribose) polymerase (PARP) and caspase-3 are up-regulated in Rh41 cells treated with BMS-536924. [3]

Oral administration of BMS-536924 at 100-300 mpk strongly inhibits IGR-1R Sal tumor model. Efficacy is also observed in the nonengineered Colo205 human colon carcinoma mode. Oral administration of 3 on a once a day schedule (100-300 mpk) or a twice a day schedule (50, 100 mpk) demonstrates antitumor activity in this tumor model. Oral glucose tolerance test (OGTT) shows 100 mpk (b.i.d.) causes a significant elevation in glucose levels after glucose challenge. The pharmacokinetic parameters of BMS-536924, administered orally in poly(ethylene glycol) 400 and water (80:20 v/v), are determined in mouse, rat, dog, and monkey. Good bioavailability is evident in all species. Significant nonlinear pharmacokinetics is observed in rodents at increasing p.o. dose. [1] BMS-536924 reduces the tumor xenografts volume of CD8-IGF-1R-MCF10A cells after two weeks' treatment (100mg/kg) to 76%. [2] Oral administration of 70 mg/kg BMS-536924 significantly inhibits tumor growth (TGBC-1TKB cells) inoculated in nude mice. BMS-536924 up regulates apoptosis in xenografts tumors. The treatment doesn't have adverse effects on the body weight of mice or the glucose levels at the time of death, suggesting tolerable toxicity. [4]

References

[1] Wittman M, et al. J Med Chem, 2005, 48(18), 5639-5643

[2] Litzenburger BC, et al. Clin Cancer Res, 2009, 15(1), 226-237

[3] Huang F, et al. Cancer Res, 2009, 69(1), 161-170

[4] Hirokazu Ohashi, et al. Cancer Sci, 2012, 103(2), 252-261

[5] Haluska P, et al, Mol Cancer THer, 2008, 7(9), 2589-2598.

[6] Huang F, et al, Cancer Res, 2009, 69(1), 161-170.

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