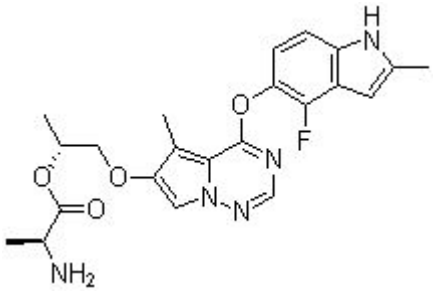
Product Introduction

Brivanib Alaninate (BMS-582664)

Brivanib alaninate (BMS-582664) is the prodrug of BMS-540215, an ATP-competitive inhibitor against **VEGFR2** with **IC50** of 25 nM.

Technical Data:

Molecular Weight (MW):	441.46	
Formula:	$C_{22}H_{24}FN_5O_4$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 88 mg/mL	
	Water <1 mg/mL	
	Ethanol 88 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	649735-63-7	

Biological Activity

BMS-582664 inhibits VEGF-stimulated and FGF-stimulated proliferating of HUVECs with IC50 of 40 nM and 276 nM. [1] BMS-582664 (2 μM) significantly inhibits VEGFR2, FGFR1, ERK1/2 and Akt phosphorylation in VEGF- and bFGF-stimulated SK-HEP1 cells and HepG-2 cells, while BMS-582664 alone has little effect on levels of phosphorylated ERK1/2, Akt, VEGFR2, and FGFR1 in nonstimulated cells. [2] BMS-582664 inhibits CYP2C19, CYP3A4(BFC) and CYP3A4 (BzRes) with IC50 of 2.4 μM, 0.51 μM and 1.6 μM, respectively. BMS-582664 exhibits high solid state stability (only 0.3% degradation at 50℃ with desiccant over a period

of 12 weeks) and acceptable solution state stability up to pH 6.5. [3]

BMS-582664 (50 mg/kg) results in AUC of 136 μM×hr and C_{max} of 41 μM in mouse. BMS-582664 (60 mg/kg, orally) is rapidly absorbed with T_{max} of 1 hour, a favorable half-life ($t_{1/2}$) of 2.7 hours and mean residence time (MRT) of 3.6 hours in mouse. BMS-582664 (25 mg/kg) results in AUC of 13.4 μM×hr and Cmax of 6.4 μM in rat. BMS-582664 dose-dependently inhibits the growth of established tumors with tumor growth inhibition of 85% and 97% at dose of 60 mg/kg and 90 mg/kg in H3396 xenografts athymic mice. [1] BMS-582664 inhibits the growth rate of tumors in mice with patient-derived xenograft line 06-0606 by 55% and 13% at dose of 50 mg/kg and 100 mg/kg. BMS-582664 (60 mg/kg, orally) significantly reduces tumor weight at sacrifice, increases apoptosis, reduces microvessel density, inhibits of cell proliferation, and down-regulates cell cycle regulators in mice with patient-derived xenograft line 06-0606. [2] BMS-582664 dose-dependently inhibits the growth of established tumors with tumor growth inhibition of 85% and 97% at dose of 80 mg/kg and 107 mg/kg in a L2987 nonsmall cell lung tumor xenografts assay in athymic mice. [3] BMS-582664 (100 mg/kg) significantly modulates tyrosine kinase receptor 1 (Tie-1), collagen type IV alpha1 (Col4a1), complement component 1, q subcomponent receptor 1 (C1qr1), angiotensin receptor-like 1 (Agtrl1), and vascular endothelial-cadherin (Cdh5) in L2987 nonsmall cell lung tumor xenografts assay in athymic mice. BMS-582664 (100 mg/kg) inhibits the new growth of endothelial cells in two xenografts mouse models, L2987 and HCT116. [4]

Alanine prodrug of BMS-540215.

References

[1] Bhide RS, et al. J Med Chem, 2006, 49(7), 2143-2146.

[2] Huynh H, et al. Clin Cancer Res, 2008, 14(19), 6146-6153.

[3] Cai ZW, et al. J Med Chem, 2008 , 51(6), 1976-1980.

[4] Ayers M, et al. Cancer Res, 2007, 67(14), 6899-6906.

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