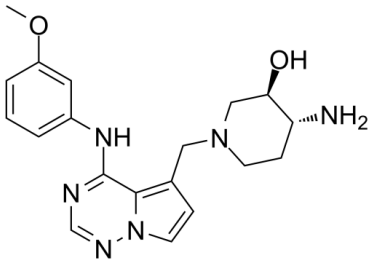
Data Sheet

Product Name:	BMS-690514
Cat. No.:	CS-0244
CAS No.:	859853-30-8
Molecular Formula:	C19H24N6O2
Molecular Weight:	368.43
Target:	EGFR; VEGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 25 mg/mL (67.86 mM)



BIOLOGICAL ACTIVITY:

BMS-690514 is a potent and orally active inhibitor of **EGFR** and **VEGFR**; has **IC_{50}**s of 5, 20 and 60 nM for EGFR, HER 2 and HER 4, respectively. IC50 & Target: IC50: 5 nM (EGFR), 20 nM (HER2), 60 nM (HER4)[1] **In Vitro:** BMS-690514 targets several critical signaling pathways: human epidermal growth factor receptor (HER)/ErbB, angiogenesis signaling through VEGFR2, lymphangiogenesis through VEGFR3, and also shows activity against VEGFR1, Flt-3, and Lck. Permeability of BMS-690514 in Caco-2 cells is in the intermediate range with a moderate potential to be a P-gp substrate[2]. BMS-690514 inhibits members of the VEGFR family with IC_{50} values in the range of 25 to 50 nM. Non–small cell lung tumor cells with exon 19 deletion (HCC4006, HCC827, and PC9) are highly sensitive to BMS-690514, which inhibits their proliferation with IC_{50} values of 2 to 35 nM. Tumor cell lines with EGFR gene amplification (DiFi, NCI-H2073, A431) are also highly sensitive to inhibition by BMS-690514. Tumor cell lines that are dependent on HER2 signaling are also found to be highly sensitive to BMS-690514. Breast and gastric tumor cell lines that have HER2 gene amplification (N87, SNU-216, AU565, BT474, KPL4, and HCC202) are inhibited with IC_{50} values of 20 to 60 nM[1]. **In Vivo:** BMS-690514 has been shown to be efficacious in a broad spectrum of tumor xenografts. At doses that are efficacious and well tolerated in the animal models, BMS-690514 inhibits tumor cell proliferation and tumor blood flow[1]. The oral bioavailability of BMS-690514 is 78% in mice, 100% in rats, 8% in monkeys, and 29% in dogs. BMS-690514 is able to cross the blood–brain barrier with a brain-to-plasma ratio of 1. The preclinical ADME properties of BMS-690514 suggest good oral bioavailability in humans and metabolism by multiple pathways including oxidation and glucuronidation[2].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: [2]Rats: BMS-690514 is administered to male Sprague–Dawley rats as a 10 min infusion intraarterially (IA) (1 mg/kg) or orally by gavage (10mg/kg). Vehicles used for dosing are: IA, 10mM acetate buffer (pH 5.0, 1 mL/kg) and PO, PEG400/10mM acetate buffer (pH 5.0, 2 mL/kg) (10:90). Serial plasma samples are obtained predose and at 0.17 (or 0.25 for PO), 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h postdose. Rats are fasted overnight and fed 4 h postdose. The brain uptake of BMS-690514 is investigated after the last dose in a 2-week toxicology study (3, 10, and 30 mg/kg/day). Brain samples are weighed and homogenized in 3 volumes of ice-chilled water. Concentrations of BMS-690514 in plasma and brain homogenates are determined by LC/MS/MS[2].

Mice: The pharmacokinetics of BMS-690514 is investigated in male balb-c mice. A total of 18 mice are divided into two groups to receive BMS-690514 as a single dose of 1mg/kg IV bolus or 5 mg/kg orally by gavage. The vehicle used for both IV (0.1mL/mouse) and PO (0.2mL/mouse) dose is Tween-80/PG/water (10:40:50). Serum concentrations of BMS-690514 are measured at 0.05 (or 0.25 for PO), 0.5, 1, 3, 6, 8, and 24 h postdose. The mice are fasted overnight and fed 6 h after dosing. Three blood samples are taken from each mouse by retro-orbital bleeding and there are three mice per time point. At the 24h time point only one sample is taken from each of the three mice. Composite serum concentration–time profiles are constructed for pharmacokinetic analysis[2].

References:

[1]. Wong TW, et al. Antitumor and antiangiogenic activities of BMS-690514, an inhibitor of human EGF and VEGF receptor kinase families. Clin Cancer Res. 2011 Jun 15;17(12):4031-41.

[2]. Marathe P, et al. Preclinical pharmacokinetics and in vitro metabolism of BMS-690514, a potent inhibitor of EGFR and VEGFR2. J Pharm Sci. 2010 Aug;99(8):3579-93.

CAIndexNames:

3-Piperidinol, 4-amino-1-[[4-[(3-methoxyphenyl)amino]pyrrolo[2,1-f][1,2,4]triazin-5-yl]methyl]-, (3R,4R)-

SMILES:

O[C@@H]1CN(CC[C@H]1N)CC2=C3C(NC4=CC=CC(OC)=C4)=NC=NN3C=C2

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