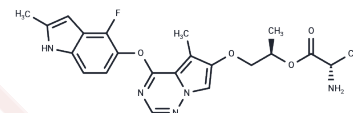


## Brivanib (alaninate)

## Chemical Properties

CAS No. :	649735-63-7
Formula:	C22H24FN5O4
Molecular Weight:	441.46
Storage:	Powder: -20°C for 3 years   In solvent: -80°C for 1 year Actual storage temperature shall be subject to the COA.



## Biological Description

Description	Brivanib Alaninate (BMS-582664) is the alaninate salt of a vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor with potential antineoplastic activity. Brivanib strongly binds to and inhibits VEGFR2, a tyrosine kinase receptor expressed almost exclusively on vascular endothelial cells; inhibition of VEGFR2 may result in inhibition of tumor angiogenesis, inhibition of tumor cell growth, and tumor regression.
Targets(IC50)	FGFR, Autophagy, VEGFR
In vitro	In rats, administration of 25 mg/kg BMS-582664 resulted in an area under the curve (AUC) of 13.4 $\mu\text{M}\times\text{hr}$ and a peak concentration ( $C_{\text{max}}$ ) of 6.4 $\mu\text{M}$ . In mice, 50 mg/kg BMS-582664 achieved an AUC of 136 $\mu\text{M}\times\text{hr}$ and a $C_{\text{max}}$ of 41 $\mu\text{M}$ . At doses of 50 mg/kg and 100 mg/kg, BMS-582664 inhibited tumor growth rates by 55% and 13%, respectively, in mice bearing patient-derived xenograft tumor 06-0606. Oral administration of 60 mg/kg BMS-582664 significantly reduced tumor weight, promoted apoptosis, decreased microvascular density, inhibited cell proliferation, and downregulated cell cycle regulation in mice with patient-derived xenograft tumor 06-0606. Mice administered 60 mg/kg BMS-582664 orally displayed rapid absorption with a maximum concentration time ( $T_{\text{max}}$ ) of 1 hour, a half-life ( $t_{1/2}$ ) of 2.7 hours, and a mean residence time of 3.6 hours. The growth of H3396 xenograft tumors in athymic mice was dose-dependently inhibited by 60 mg/kg and 90 mg/kg BMS-582664, with tumor growth inhibition rates of 85% and 97%, respectively. Doses of 80 mg/kg and 107 mg/kg BMS-582664 dose-dependently inhibited tumor growth in athymic mice bearing L2987 non-small cell lung cancer xenograft tumors, with tumor growth inhibition rates of 85% and 97%, respectively. At a dose of 100 mg/kg, BMS-582664 inhibited the growth of endothelial cells in two mouse xenograft models (L2987 and HCT116).
In vivo	BMS-582664 exhibits high solid stability, with only 0.3% degradation after a 12-cycle period at 50°C in the presence of desiccants and good liquid stability at pH 6.5. At 2 $\mu\text{M}$ concentration, BMS-582664 significantly inhibits the phosphorylation of VEGFR-2, FGFR-1, ERK1/2, and Akt in SK-HEP1 and HepG-2 cells stimulated by VEGF and bFGF, without affecting the phosphorylation levels in unstimulated cells. It also inhibits the proliferation of HUVECs stimulated by VEGF and FGF, with $\text{IC}_{50}$ values of 40 nM and 276 nM, respectively. Furthermore, BMS-582664 inhibits the enzymes CYP2C19, CYP3A4(BFC), and CYP3A4 (BzRes), with $\text{IC}_{50}$ values of 2.4 $\mu\text{M}$ , 0.51 $\mu\text{M}$ , and 1.6 $\mu\text{M}$ , respectively.
Kinase Assay	Kinase inhibition assays: For the VEGFR2, Flk1 and FGFR1 kinase assays, BMS-582664 is dissolved in DMSO and diluted with water/10% DMSO to a final DMSO concentration of

Kinase Assay	2%. The kinase reactions consists of 8 ng of enzymes with GST tag, 75 µg/mL substrate, 1 µM ATP, and 0.04 µCi [ $\gamma$ - <sup>33</sup> P]ATP in 50 µL total reaction volume (kinase buffer: 20 mM Tris, pH 7.0, 25 µg/mL BSA, 1.5 mM MnCl <sub>2</sub> , 0.5 mM dithiothreitol). In all cases, the reactions are incubated for 60 min at 27°C and terminated with the addition of cold trichloroacetic acid (TCA) to a final concentration of 15%. The percent inhibition from the kinase assays is determined by nonlinear regression analyses, and data are reported as the inhibitory concentration required to achieve 50% inhibition relative to control reactions (IC <sub>50</sub> ).
Cell Research	Cells are grown in 100 µL of minimal growth medium and 1.0% heat-inactivated fetal bovine serum in 96-well collagen IV coated plates at a density of 2 × 10 <sup>3</sup> per well in a 37 °C/5% CO <sub>2</sub> environment. Twenty-four hours later, serum is adjusted to 10%, and BMS-582664 at various dilutions are added to each well in a final volume of minimal growth media that contains 10% serum. Forty-eight hours later, 0.5 µCi of [ <sup>3</sup> H]thymidine is added in a volume of 20 µL of minimal media for 24 hours. Plates are washed once in PBS. Upon removal of PBS, Trypsin is added to cells which are subsequently harvested onto glass-fiber filters using an automated harvester. Incorporated tritium is quantified using a β-counter. Dose-response curves are generated to determine the IC <sub>50</sub> value, which is defined as the concentration of drug required to inhibit 50% of tritium incorporation when compared to untreated serum-stimulated cells.(Only for Reference)

### Solubility Information

Solubility	Ethanol: 82 mg/mL (185.75 mM),Sonication is recommended. DMSO: 82 mg/mL (185.75 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+90% Corn Oil: 3.3 mg/mL (7.48 mM),Sonication is recommended. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

### Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.2652 mL	11.3261 mL	22.6521 mL
5 mM	0.453 mL	2.2652 mL	4.5304 mL
10 mM	0.2265 mL	1.1326 mL	2.2652 mL
50 mM	0.0453 mL	0.2265 mL	0.453 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

### Reference

- Bhide RS, et al. J Med Chem, 2006, 49(7), 2143-2146.  
 Huynh H, et al. Clin Cancer Res, 2008, 14(19), 6146-6153.  
 Cai ZW, et al. J Med Chem, 2008, 51(6), 1976-1980.  
 Ayers M, et al. Cancer Res, 2007, 67(14), 6899-6906.

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