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产品名称：Brivanib Alaninate (BMS-582664)
产品别名：丙氨酸布立尼布

生物活性：

Description	Brivanib alaninate is an ATP-competitive inhibitor against VEGFR2 with an IC50 of 25 nM; has moderate potency against VEGFR-1 and FGFR-1, but more than 240-fold against PDGFRβ.
IC_{50} & Target	VEGFR2
	25 nM (IC_{50})
In Vitro	Brivanib inhibits VEGFR1 and FGFR-1 with IC_{50} of 0.38 μM and 0.148 μM. Brivanib is not sensitive to PDGFRβ, EGFR, LCK, PKCα or JAK-3 with IC_{50} all above 1900 nM. Brivanib could inhibit the proliferation of VEGF-stimulated HUVECs with IC_{50} of 40 nM, compared to 276 nM in FGF-stimulated HUVECs. On the other hand, brivanib exhibits low activity to tumor cell lines[1]. Brivanib doses ≤20 μM paradoxically enhances FGF-induced LX-2 cell proliferation, whereas higher brivanib doses (≥30 μM) inhibits LX-2 cell proliferation. The inhibitory effect of brivanib on liver fibrosis is not through inhibition of TGF-β 1-induced stellate cell activation, and is possibly through inhibition of PDGF-BB-induced stellate cell activation[3].
In Vivo	Brivanib displays antitumor activities in H3396 xenograft in athymic mice. At a dose of 60 and 90 mg/kg (p.o.), brivanib completely inhibits the tumor growth, with TGI of 85% and 97%, respectively[1]. Moreover, brivanib significantly suppresses tumor growth in Hepatocellular carcinoma (HCC) xenografts, which due to the decrease in phosphorylation of VEGFR2. The results show that the tumor weights in 06-0606 xenograft mice are 55% and 13%, compared with the controls at a dose of 50 mg/kg and 100 mg/kg. Brivanib is suggested to be efficient in treatment of HCC[2]. Brivanib (50 mg/kg, p.o.) attenuates liver fibrosis and stellate cell activation induced by BDL in mice. Brivanib inhibits growth factor and growth factor receptor mRNA expression in sham control animals but shows variable effects in bile duct ligated animals[3].
Solvent&Solubility	***In Vitro:***
	DMSO : ≥ 100 mg/mL (226.52 mM)
	* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2652 mL	11.3261 mL	22.6521 mL
5 mM	0.4530 mL	2.2652 mL	4.5304 mL
10 mM	0.2265 mL	1.1326 mL	2.2652 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

	1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (5.66 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.66 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (5.66 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.66 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.66 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.66 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Bhide RS, et al. Discovery and preclinical studies of (R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan- 2-ol (BMS-540215), an in vivo active potent VEGFR-2 inhibitor. J Med Chem, 2006, 49 (7), 2143-2146. [2]. Nakamura I, et al. Correction: Brivanib Attenuates Hepatic Fibrosis In Vivo and Stellate Cell Activation In Vitro by Inhibition of FGF, VEGF and PDGF Signaling. PLoS One. 2015 Nov 3;10(11):e0142355. [3]. Huynh H, et al. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. Clin Cancer Res, 2008, 14(19), 6146-6153.

实验参考：

Cell Assay	Viability is measured in LX-2 cells using the Cell Counting Kit-8 (CCK-8). Using 96-well plates with 2,000 cells per well, HSCs are incubated in 10% FBS-supplemented DMEM for 24 hours, followed by starvation in serum-free media. After 24 hours of starvation, brivanib is added at different doses. Two hours later, 5 ng/mL PDGF-BB is added. The cells are incubated for an additional 72 hours and cell viability is measured. Each experiment is performed in three replicates at least four times[3].
Animal Administration	Male mice 4-6 weeks of age are treated 3 times a week with a total of 12 intraperitoneal (i.p.) injections of 150 mL/kg TAA. At the onset of TAA treatment, placebo or brivanib (25 or 50 mg/kg) is administered orally on 5 consecutive days with weekend breaks. The animals are sacrificed 4 weeks after the start of the injections[3].
References	[1]. Bhide RS, et al. Discovery and preclinical studies of (R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5- methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-ol (BMS-540215), an in vivo active potent VEGFR-2 inhibitor. J Med Chem, 2006, 49 (7), 2143-2146. [2]. Nakamura I, et al. Correction: Brivanib Attenuates Hepatic Fibrosis In Vivo and Stellate Cell

	Activation In Vitro by Inhibition of FGF, VEGF and PDGF Signaling. PLoS One. 2015 Nov 3;10(11):e0142355. [3]. Huynh H, et al. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. Clin Cancer Res, 2008, 14(19), 6146-6153.