产品名称：**SB590885**
产品别名：**SB-590885**

生物活性：

Description	SB-590885 is a potent B-Raf inhibitor with K_i of 0.16 nM, and has 11-fold greater selectivity for B-Raf over c-Raf, without inhibition to other human kinases.

IC_{50} & Target [1]	B-Raf	c-Raf
	0.16 nM (Ki)	1.72 nM (Ki)

In Vitro

SB-590885 displays significant selectivity for B-Raf over c-Raf with Ki of 0.16 nM over 1.72 nM. SB-590885 is a more potent inhibitor than the previously described Raf/VEGFR kinase inhibitor BAY 439006 (Ki=38 nM for mutant B-Raf, 6 nM for c-Raf). SB-590885 displays potent selectivity over 46 other kinases. Unlike the multi-kinase inhibitor BAY43-9006, SB-590885 stabilizes the oncogenic B-Raf kinase domain in an active configuration. In Colo205, HT29, A375P, SKMEL28, and MALME-3M cells expressing oncogenic B-RafV600E, SB-590885 treatment potently inhibits ERK phosphorylation with EC50 of 28 nM, 58 nM, 290 nM, 58 nM, and 190 nM, respectively, and consistently, inhibits the proliferation with EC50 of 0.1 μM, 0.87 μM, 0.37 μM, 0.12 μM, and 0.15 μM, respectively. SB-590885 decreases anchorage-independent growth of melanoma cell lines in a BRAF mutant-selective manner[1]. SB-590885 displays high affinity for B-Raf with Kd of 0.3 nM[2]. Most of the melanoma cell lines that harbor the BRAF V600E mutation and lack CDK4 mutations (451Lu, WM35, and WM983) are highly sensitive to SB-590885 with IC50 of <1 μM. Increased levels of cyclin D1 resulting from genomic amplification mediate SB-590885 resistance in B-Raf V600E-mutated melanomas[3].

In Vivo

Administration of SB-590885 potently decreases tumorigenesis in murine xenografts established from mutant B-Raf-expressing A375P melanoma cells, and modestly inhibits tumor growth[1].

Solvent&Solubility

In Vitro:

DMSO : 33.33 mg/mL (**73.49 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2049 mL	11.0244 mL	22.0488 mL
	5 mM	0.4410 mL	2.2049 mL	4.4098 mL
	10 mM	0.2205 mL	1.1024 mL	2.2049 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 (5.51 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.51 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 (5.51 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.51 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 (5.51 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.51 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]. King AJ, et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. Cancer Res, 2006, 66(23), 11100-11105. [2]. Takle AK, et al. The identification of potent and selective imidazole-based inhibitors of B-Raf kinase. Bioorg Med Chem Lett, 2006, 16(2), 378-381. [3]. Smalley KS, et al. Increased cyclin D1 expression can mediate BRAF inhibitor resistance in BRAF V600E-mutated melanomas. Mol Cancer Ther, 2008, 7(9), 2876-2883.

实验参考：

Cell Assay	For proliferation assays, cells are treated with compounds in 0.1% DMSO and incubated for 72 hours at 37°C, 5% CO_2. Viable cells are quantified using CellTiter-Glo reagent and luminescence detection on a Victor 2V plate reader. Cells are prepared for cell cycle analysis on a Becton Dickinson FACScan, according to the manufacturer's instructions. Data is acquired and analyzed using CellQuest v3.3 software. Anchorage-independent growth assays are done as described elsewhere, with inhibitors or DMSO vehicle included in the agar layer. Cultures are re-fed with media and inhibitor or DMSO every 5 to 7 days for a total of 28 days. Colonies are visualized and photographed by conventional light microscopy and quantified by counting on a grid in triplicate. [1]
Animal Administration	The pharmacokinetic properties and safety of SB-590885, following i.p. injection, are determined and 50 mg/kg daily injections are found to give therapeutic levels with minimal body weight changes. Tumors are initiated in 8- to 12-week-old female nude mice by s.c. injection of 5×10^6 A375P cells in Matrigel suspension, and 3 weeks after tumor induction when the tumors had reached a volume of 150 to 250 mm^3, mice are randomized into groups of eight prior to treatment. Animals are treated with vehicle [2% N,N-dimethylacetamide, 2% Cremophor EL, and 96% acidified water (pH 4-5)], or vehicle containing 50 mg/kg of SB-590885 daily for 21 days. A cohort of mice treated with SB-590885 are then observed an additional 14 days following cessation of treatment. Tumor volume is measured for 55 days by calipers twice weekly. [1]
References	[1]. King AJ, et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. Cancer Res, 2006, 66(23), 11100-11105. [2]. Takle AK, et al. The identification of potent and selective imidazole-based inhibitors of B-Raf kinase. Bioorg Med Chem Lett, 2006, 16(2), 378-381.

	[3]. Smalley KS, et al. Increased cyclin D1 expression can mediate BRAF inhibitor resistance in BRAF V600E-mutated melanomas. Mol Cancer Ther, 2008, 7(9), 2876-2883.