产品名称：**SB1317**
产品别名：**TG02**

生物活性：

Description

SB1317 is a potent inhibitor of CDK2, JAK2, and FLT3 for the treatment of cancer, with IC_{50} of 13, 73, and 56 nM for CDK2, JAK2 and FLT3, respectively.

IC_{50} & Target

CDK2	JAK2	FLT3
13 nM (IC_{50})	73 nM (IC_{50})	56 nM (IC_{50})

In Vitro

SB1317 has a highly novel kinase inhibitory spectrum inhibiting 17 kinases from a panel of 63, 11 of which are CDK/JAK/FLT family members. The others, Lck, Fyn, Fms, TYRO3, ERK5, and p38δ, are implicated in inflammatory and proliferative processes. Human CYP1A2, 3A4, 2C9, and 2C19 isoforms are not inhibited by SB1317 at the highest tested concentration of 25 μM, but SB1317 inhibits CYP2D6 with IC_{50}=0.95 μM, approximately at the plasma C_{max} observed at the maximum tolerated dose. SB1317 inhibits cell proliferation concentrations in HCT-116 (IC_{50}=0.079 μM) and HL-60 (IC_{50}=0.059 μM) [1]. SB1317 is a novel small molecule potent CDK/JAK2/FLT3 inhibitor. SB1317 is mainly metabolized by CYP3A4 and CY1A2 in vitro. SB1317 does not inhibit any of the major human CYPs in vitro except CYP2D6 (IC_{50}=1 μM). SB1317 does not significantly induce CYP1A and CYP3A4 in human hepatocytes in vitro[2].

In Vivo

Treatment with SB1317 at 75 mg/kg po q.d. 3×/week significantly inhibits the growth of tumors with a mean TGI of 82%, while the lower dose of 50 mg/kg po 3×/week is marginally effective. Treatment with SB1317 using either regime significantly inhibits the growth of tumors with mean TGIs of 42% and 63% for the oral and ip delivery methods, respectively[1]. In pharmacokinetic studies SB1317 shows moderate to high systemic clearance (relative to liver blood flow), high volume of distribution (>0.6 L/kg), oral bioavailability of 24%, ~4 and 37% in mice, rats and dogs, respectively; and extensive tissue distribution in mice[2].

Solvent&Solubility

In Vitro:

DMSO : 26.5 mg/mL (71.15 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6849 mL	13.4243 mL	26.8485 mL
	5 mM	0.5370 mL	2.6849 mL	5.3697 mL
	10 mM	0.2685 mL	1.3424 mL	2.6849 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: ≥ 2.08 mg/mL (5.58 mM); Clear solution

此方案可获得 ≥ 2.08 mg/mL (5.58 mM，饱和度未知) 的澄清溶液。

	以 1 mL 工作液为例，取 100 μL 20.8 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: ≥ 2.08 mg/mL (5.58 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (5.58 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 20.8 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。
References	[1]. William AD, et al. Discovery of kinase spectrum selective macrocycle (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene (SB1317/TG02), a potent inhibitor of cyclin dependent kina [2]. Pasha MK, et al. Preclinical metabolism and pharmacokinetics of SB1317 (TG02), a potent CDK/JAK2/FLT3 inhibitor. Drug Metab Lett. 2012 Mar;6(1):33-42.

实验参考：

Cell Assay	All cell lines are obtained from the American Type Culture Collection and cultured. For proliferation assays in 96-well plates, 20 000 cells are seeded in 100 μL of medium and treated the following day with compounds (e.g., SB1317) (in triplicate) at concentrations up to 10 μM for 48 h. Cell viability is monitored using the CellTiter-96 Aqueous One solution cell proliferation assay. Dose-response curves are plotted to determine IC_{50} values for the compounds using the XL-fit software[1]
Animal Administration	Mice and Rats[1] Male BALB/c mice (aged ~10-12 weeks and weighing 17-22 g), male Beagle dogs (~6-7 months of age, weighing 10-14 kg), and male Wistar rats (aged 6-8 weeks, weighing 239-249 g) are used in this study. The oral doses for mice, dogs, and rats are 75, 10, and 10 mg/kg, respectively. The doses are administered by gavage as suspensions (0.5% methylcellulose and 0.1% Tween 80) to mice and rats, and as gelatin capsules (12 Torpac) to dogs. Following oral dosing serial blood samples are collected (cardiac puncture in mice, jugular vein in dogs, and superior vena cava in rats) at different time points (0-24 h) in tubes containing K_3EDTA as anticoagulant, centrifuged, and plasma is separated and stored at -70°C until analysis. Plasma samples are processed and analyzed by LC-MS/MS. Pharmacokinetic parameters are estimated by noncompartmental methods using WinNonlin.
Kinase Assay	The recombinant enzymes (CDK2/cyclin A, JAK2, and FLT3) are used. All assays are carried out in 384-well white microtiter plates using the PKLight assay system. This assay platform is a luminometric assay for the detection of ATP in the reaction using a luciferase-coupled reaction. The compounds are tested at eight concentrations prepared from 3- or 4-fold serial dilution starting at 10 μM. For CDK2/cyclin A assay, the reaction mixture consisted of the following components in 25 μL of assay buffer (50 mM Hepes, pH 7.5, 10 mM $MgCl_2$, 5 mM $MnCl_2$, 5 mM BGP, 1 mM DTT, 0.1 mM sodium orthovanadate), 1.4 μg/mL of CDK2/cyclin A complex, 0.5 μM RbING substrate, and 0.5 μM ATP. The mixture is incubated at room temperature for 2 h. Then 13 μL of PKLight ATP detection reagent is added and the mixture is incubated for 10 min. Luminescence signals are detected on a multilabel plate reader. The analytical software Prism 5.0 is used to generate IC_{50} values from the data[1]
	[1]. William AD, et al. Discovery of kinase spectrum selective macrocycle (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,

References	5,8(27),9,11,16,21,23-decaene (SB1317/TG02), a potent inhibitor of cyclin dependent kina [2]. Pasha MK, et al. Preclinical metabolism and pharmacokinetics of SB1317 (TG02), a potent CDK/JAK2/FLT3 inhibitor. Drug Metab Lett. 2012 Mar;6(1):33-42.