产品名称：CEP-33779
产品别名：CEP-33779

生物活性：

Description	CEP-33779 is a novel, selective, and orally bioavailable inhibitor of **JAK2** with an **IC_{50}** of 1.8±0.6 nM.	
IC_{50} & Target	JAK2	JAK3
	1.8 nM (IC_{50})	150 nM (IC_{50})
In Vitro	CEP-33779, at nontoxic concentrations, significantly sensitizes overexpression of P-glycoprotein overexpressing multidrug resistance cells to its anticancer substrates. CEP-33779 significantly increases intracellular accumulation and decreases the efflux of doxorubicin by inhibiting the overexpression of P-glycoprotein transport function[3].	
In Vivo	CEP-33779 exhibits a favorable PK profile in nude mice, an iv half-life of 1 h, moderate distribution (Vd=2.6 L/kg), and measurable oral exposure with an estimated bioavailability of 33%. It demonstrates antitumor efficacy in the CWR22 xenograft model; oral dosing for 14 days at 30 mg/kg bid results in tumor stasis and partial regressions in 5/10 animals[1]. CEP-33779 administration results in an almost complete shrinkage of tumors in most animals; few remaining tumor nodules were small, poorly vascularized, and had a necrotic appearance. CEP-33779 suppressed activation of NF-κB in tumors[2].	

Solvent&Solubility

In Vitro:

DMSO : 50 mg/mL (**108.09 mM;** Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1618 mL	10.8092 mL	21.6183 mL
	5 mM	0.4324 mL	2.1618 mL	4.3237 mL
	10 mM	0.2162 mL	1.0809 mL	2.1618 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 (5.40 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.40 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 (5.40 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.40 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 (5.40 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.40 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]. Dugan BJ, et al. A selective, orally bioavailable 1,2,4-triazolo[1,5-a]pyridine-based inhibitor of Janus kinase 2 for use in anticancer therapy: discovery of CEP-33779. J Med Chem. 2012 Jun 14;55(11):5243-54. [2]. Seavey MM, et al. Therapeutic efficacy of CEP-33779, a novel selective JAK2 inhibitor, in a mouse model of colitis-induced colorectal cancer. Mol Cancer Ther. 2012 Apr;11(4):984-93. [3]. Tang SJ, et al. CEP-33779 antagonizes ATP-binding cassette subfamily B member 1 mediated multidrug resistance by inhibiting its transport function. Biochem Pharmacol. 2014 Sep 15;91(2):144-56.

实验参考：

Cell Assay	
Animal Administration	Mice: Nude mice bearing CWR22 xenografts are dosed orally with 55 mg/kg of CEP-33779 or a vehicle (PEG400). At 2, 6, and 24 h after dosing animals (3/group) are sacrificed, tumors are excised and plasma samples are prepared. Tumor extracts are prepared using Triton-based extraction buffer supplemented with inhibitors of proteases and phosphatases. Equal amounts of extracts are resolved on SDS-PAGE gels and STAT3 phosphorylation and expression are analyzed by Western blot using specific antibodies[1].
Kinase Assay	The kinase activity of baculovirus-expressed human JAK1, JAK2, or JAK3 is measured. Each 96-well Costar high binding plate is coated with 100 μL/well of 10 μg/mL neutravidin in TBS at 37 °C for 2 h, followed by 100 μL/well of 1 μg/mL 15-mer peptide substrate at 37 °C for 1 h. The kinase assay mixture (total volume=100 μL/well) consisting of 20 mM HEPES (pH 7.2), ATP (0.2 μM ATP for JAK1 and JAK2 and 0.1 μM ATP for JAK3), 1 mM $MnCl_2$, 0.1% BSA, and CEP-33779 (diluted in DMSO, 2.5% DMSO final in assay) is added to the assay plate. Enzyme is added and the reaction is allowed to proceed for 20 min at room temperature. Detection of the phosphorylated product is performed by adding 100 μL/well of diluted Eu-N1 labeled PY100 antibody. Samples are incubated at RT for 1 h, followed by addition of 100 μL enhancement solution. Plates are agitated for 10 min, and the fluorescence of the resulting solution is measured. IC50 values are determined[1].
References	[1]. Dugan BJ, et al. A selective, orally bioavailable 1,2,4-triazolo[1,5-a]pyridine-based inhibitor of Janus kinase 2 for use in anticancer therapy: discovery of CEP-33779. J Med Chem. 2012 Jun 14;55(11):5243-54. [2]. Seavey MM, et al. Therapeutic efficacy of CEP-33779, a novel selective JAK2 inhibitor, in a mouse model of colitis-induced colorectal cancer. Mol Cancer Ther. 2012 Apr;11(4):984-93. [3]. Tang SJ, et al. CEP-33779 antagonizes ATP-binding cassette subfamily B member 1 mediated multidrug resistance by inhibiting its transport function. Biochem Pharmacol. 2014 Sep 15;91(2):144-56.