产品名称：EED226
产品别名：EED226

生物活性：

Description	EED226 is a polycomb repressive complex 2 (PRC2) inhibitor, which binds to the K27me3-pocket on embryonic ectoderm development (EED) and shows strong antitumor activity in xenograft mice model[1]. EED226 is a potent, selective, and orally bioavailable EED inhibitor[2]. EED226 inhibits PRC2 with an IC50 of 23.4 nM when the H3K27me0 peptide is used as a substrate in the in vitro enzymatic assays[3].
IC_{50} & Target	IC50: 23.4 nM (PRC2)[3]
In Vitro	EED226 is a highly potent, efficient and selective inhibitor of EZH2 and EZH1 evaluated against a broad range of epigenetic and non-epigenetic targets. It potently reduces global H3K27Me3 mark in cells and demonstrates selectively cell killing effects in cells carrying a heterozygous Y641N mutation. EED226 has moderate permeability as the measured in Caco-2 cells at A→B=3.0x10^{-6} cm/s, with an efflux ratio at 7.6[2]. In the in vitro enzymatic assays, EED226 inhibited PRC2 with an IC50 of 53.5 nM when the mononucleosome is used as the substrate, with the stimulatory H3K27me3 added at 1× K_{act} (1.0 μM)[3].
In Vivo	EED226 induces robust and sustained tumor regression in EZH2^{MUT} pre-clinical DLBCL model. In CD-1 mice, dosing of EED226 for 14 days at 300 mg/kg bid is well tolerated with no apparent adverse effects. It has very low *in vivo* clearance, and approximately 100% oral bioavailability. EED226 has low volume of distribution (0.8 L/kg), reasonable terminal $t_{1/2}$ (2.2 h), and moderate plasma protein binding (PPB)[2].

Solvent&Solubility

In Vitro:

DMSO : ≥ 29 mg/mL (78.51 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7071 mL	13.5355 mL	27.0709 mL
	5 mM	0.5414 mL	2.7071 mL	5.4142 mL
	10 mM	0.2707 mL	1.3535 mL	2.7071 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 (6.77 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.77 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 (6.77 mM); Suspended solution 此方案可获得 ≥ 2.5 mg/mL (6.77 mM，饱和度未知) 的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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 (6.77 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.77 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]. Li L, et al. Discovery and Molecular Basis of a Diverse Set of Polycomb Repressive Complex 2 Inhibitors Recognition by EED. PLoS One. 2017 Jan 10;12(1):e0169855. [2]. Huang Y, et al. Discovery of First-in-Class, Potent, and Orally Bioavailable Embryonic Ectoderm Development (EED) Inhibitor with Robust Anticancer Efficacy. J Med Chem. 2017 Mar 23;60(6):2215-2226. [3]. Qi W, et al. An allosteric PRC2 inhibitor targeting the H3K27me3 binding pocket of EED. Nat Chem Biol. 2017 Apr;13(4):381-388.

实验参考：

Animal Administration	Mice: EED226 is formulated as a suspension in 0.5% PHMC+0.5% Tween 80 in water and administered orally by gavage at a dose volume of 10 mL/kg to the tumor bearing mice. At the end point, the animals is given the first dose administration. For PK analysis 100 μL of blood samples are collected from each animal by orbital sinus bleeding. For analysis of compound levels and PD in tissues, tumors are collected 4 hr post treatment and frozen immediately in liquid nitrogen. Tumor and body weight change data are analyzed statistically[2].
References	[1]. Li L, et al. Discovery and Molecular Basis of a Diverse Set of Polycomb Repressive Complex 2 Inhibitors Recognition by EED. PLoS One. 2017 Jan 10;12(1):e0169855. [2]. Huang Y, et al. Discovery of First-in-Class, Potent, and Orally Bioavailable Embryonic Ectoderm Development (EED) Inhibitor with Robust Anticancer Efficacy. J Med Chem. 2017 Mar 23;60(6):2215-2226. [3]. Qi W, et al. An allosteric PRC2 inhibitor targeting the H3K27me3 binding pocket of EED. Nat Chem Biol. 2017 Apr;13(4):381-388.