产品名称：**XAV-939**
产品别名：**XAV-939**

生物活性：

Description

XAV-939 is a Wnt/β-catenin pathway inhibitor. XAV-939 stabilizes axin by inhibiting the poly-ADP-ribosylating enzymes tankyrase 1 and tankyrase 2 (IC50s of 5 and 2 nM,respectively), thereby stimulating β-catenin degradation. XAV939 binds tightly to the catalytic (PARP) domains of TNKS1 and TNKS2 (Kds of 99 and 93 nM, respectively)[1].

IC_{50} & Target

TNKS2	TNKS1	ARTD2	ARTD1
2 nM (IC_{50})	5 nM (IC_{50})	479 nM (IC_{50})	5500 nM (IC_{50})

In Vitro

XAV939 also binds to recombinant PARP1, although with a significantly lower binding affinity (Kd=1.2 μM). XAV939 (1 μM) strongly inhibis STF activity in SW480 cells, Wnt3a-stimulated STF activity in HEK293 cells, but does not affect CRE, NF-κB or TGF-β luciferase reporters. XAV939 regulates axin levels through tankyrase inhibition in HEK293 cell[1]. XAV939 (0.5 μM, 1.0 μM) reduces DNA-PKcs protein levels 50% of the relative DMSO control in human lymphoblasts[2]. XAV939 induces a second wave of pro-cardiomyocyte gene expression as shown by increased Mesp1 and Isl1expression 2 to 4 days after Wnt inhibition, and by increased Nkx2.5 expression 4 to 6 days after XAV939 addition[3]. XAV-939 (10 nM) has a suppressive effect on elevated MMP-13 levels in both IL-1β-induced SW 1353 cells[4].

In Vivo

XAV-939 (3 mL, 10 nM) has a suppressive effect on elevated MMP-13 levels in the rat OA model[4]. XAV-939 (1 mg/mL, i.p.) ameliorates the psoriasiform skin disease induced by IMQ. XAV-939 results in a significant decrease in the IMQ-induced epidermal hyperplasia (indicated by acanthosis) and dermal inflammatory infiltrates in mice[5].

Solvent&Solubility

In Vitro:

DMSO : 21.5 mg/mL (**68.84 mM;** Need ultrasonic and warming)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2019 mL	16.0097 mL	32.0195 mL
	5 mM	0.6404 mL	3.2019 mL	6.4039 mL
	10 mM	0.3202 mL	1.6010 mL	3.2019 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 mg/mL (6.40 mM); Suspended solution; Need ultrasonic

此方案可获得 2 mg/mL (6.40 mM)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 20.0 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 mg/mL (6.40 mM); Suspended solution; Need ultrasonic 此方案可获得 2 mg/mL (6.40 mM)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 20.0 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 mg/mL (6.40 mM); Clear solution 此方案可获得 ≥ 2 mg/mL (6.40 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 20.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Huang SM, et al. Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. Nature. 2009 Oct 1;461(7264):614-620. [2]. Dregalla RC, et al. Regulatory roles of tankyrase 1 at telomeres and in DNA repair: suppression of T-SCE and stabilization of DNA-PKcs. Aging (Albany NY). 2010 Oct;2(10):691-708. [3]. Ao A, et al. DMH1, a Novel BMP Small Molecule Inhibitor, Increases Cardiomyocyte Progenitors and Promotes Cardiac Differentiation in Mouse Embryonic Stem Cells.,PLoS One. 2012;7(7):e41627. [4]. Zeng L, et al. Chondroprotective effects and multi-target mechanisms of Icariin in IL-1 beta-induced human SW 1353 chondrosarcoma cells and a rat osteoarthritis model. Int Immunopharmacol. 2014 Jan;18(1):175-81. [5]. Bai J, et al. Epigenetic downregulation of SFRP4 contributes to epidermal hyperplasia in psoriasis. J Immunol. 2015 May 1;194(9):4185-98. doi: 10.4049/jimmunol.1403196. Epub 2015 Mar 30. [6]. Narwal M, et al. Discovery of tankyrase inhibiting flavones with increased potency and isoenzyme selectivity. J Med Chem. 2013 Oct 24;56(20):7880-9. [7]. Liu D, et al. Wnt/β-catenin signaling participates in the regulation of lipogenesis in the liver of juvenile turbot (Scophthalmus maximus L.). Comp Biochem Physiol B Biochem Mol Biol. 2016 Jan;191:155-62.

实验参考：

Cell Assay	Human SW 1353 chondrosarcoma cells are seeded in 96-well plates (1×10^4 cells/well) and are treated with Icariin (0, 5, 10, 20, 40, 80, or 100 μM). After 24 h, 20 μL MTT (5 mg/mL in PBS) is added to each well and plates are incubated at 37°C for another 4 h. Supernatants are then removed, and 150 μL DMSO is added to each well. After plates are shaken for 10 min, optical density values measured at 570 nm are recorded using an ELISA reader. [4]
Animal Administration	C57BL/6J mice are kept under specific pathogen-free conditions. XAV-939 is injected i.p., at a dose of 1 mg/mL, once a day for seven consecutive days of IMQ treatment (injection volume 100 μL). Control mice are injected with 100 μL 10% DMSO/90% 0.9% NaCl, the solvent for XAV-939. To ameliorate any suffering of mice observed throughout these experimental studies, they are euthanized by CO_2 inhalation. [5]
	To assess the effect of compounds on auto-PARsylation of TNKS, 1 μM GST fusion protein containing the SAM domain and the PARP domain of TNKS2 (a.a. 872-1166) is mixed with 5 μM

Kinase Assay	biotin-NAD$^+$ and 2 μM XAV939 or LDW643 at 30°C for 2.5 hours. Samples are resolved by SDS-PAGE and probed with streptavidin AlexaFluor680. To assess PARsylation of axin, recombinant full-length TNKS2 (expressed/purified as a N-terminal His-tagged protein in bacteria) is incubated with GST-axin 1 (1-280) in the presence of biotin-NAD$^+$ with or without XAV939. The products are resolved and probed with Streptavidin-HRP and imaged using a AlphaInnotech imager. To assess the effect of XAV939, IWR-1-enod, IWR-1-exo, and ABT-888 on auto-PARsylation of TNKS2, His-tagged full-length TNKS2 is incubated with 5 μM biotin-NAD$^+$ and 3 mM of indicated compounds. The products are resolved and probed with Streptavidin-HRP. LC/MS-based high throughput auto-PARsylation assays for PARP1, PARP2, TNKS1, and TNKS2 are setup to monitor the formation of nicotinamide (a by-product of the PARsylation reaction) in the presence of small molecule inhibitors. [1]
References	[1]. Huang SM, et al. Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. Nature. 2009 Oct 1;461(7264):614-620. [2]. Dregalla RC, et al. Regulatory roles of tankyrase 1 at telomeres and in DNA repair: suppression of T-SCE and stabilization of DNA-PKcs. Aging (Albany NY). 2010 Oct;2(10):691-708. [3]. Ao A, et al. DMH1, a Novel BMP Small Molecule Inhibitor, Increases Cardiomyocyte Progenitors and Promotes Cardiac Differentiation in Mouse Embryonic Stem Cells.,PLoS One. 2012;7(7):e41627. [4]. Zeng L, et al. Chondroprotective effects and multi-target mechanisms of Icariin in IL-1 beta-induced human SW 1353 chondrosarcoma cells and a rat osteoarthritis model. Int Immunopharmacol. 2014 Jan;18(1):175-81. [5]. Bai J, et al. Epigenetic downregulation of SFRP4 contributes to epidermal hyperplasia in psoriasis. J Immunol. 2015 May 1;194(9):4185-98. doi: 10.4049/jimmunol.1403196. Epub 2015 Mar 30. [6]. Narwal M, et al. Discovery of tankyrase inhibiting flavones with increased potency and isoenzyme selectivity. J Med Chem. 2013 Oct 24;56(20):7880-9. [7]. Liu D, et al. Wnt/β-catenin signaling participates in the regulation of lipogenesis in the liver of juvenile turbot (Scophthalmus maximus L.). Comp Biochem Physiol B Biochem Mol Biol. 2016 Jan;191:155-62.