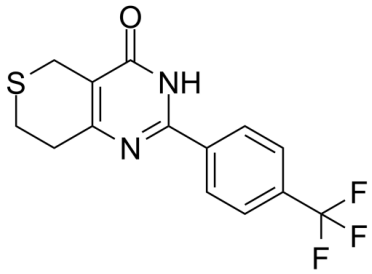
Data Sheet

Product Name:	XAV-939
Cat. No.:	CS-0494
CAS No.:	284028-89-3
Molecular Formula:	C14H11F3N2OS
Molecular Weight:	312.31
Target:	PARP; β-catenin
Pathway:	Cell Cycle/DNA Damage; Epigenetics; Stem Cell/Wnt
Solubility:	DMSO : 21.5 mg/mL (68.84 mM; Need ultrasonic and warming); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

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 (IC_{50}s of 5 and 2 nM,respectively), thereby stimulating β-catenin degradation. XAV939 binds tightly to the catalytic (PARP) domains of TNKS1 and TNKS2 (K_ds of 99 and 93 nM, respectively)[1]. IC50 & Target: IC50: 5 nM (TNKS1), 2 nM (TNKS2)[6] **In Vitro:** XAV939 also binds to recombinant PARP1, although with a significantly lower binding affinity (K_d=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].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]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 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. **Cell Assay:** XAV-939 is dissolved in DMSO.[4]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. **Animal Administration:** XAV-939 is formulated in 10% DMSO/90% 0.9% NaCl.[5]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.

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.

CAIndexNames:

4H-Thiopyrano[4,3-d]pyrimidin-4-one, 3,5,7,8-tetrahydro-2-[4-(trifluoromethyl)phenyl]-

SMILES:

O=C1C(CSCC2)=C2N=C(C3=CC=C(C(F)(F)F)C=C3)N1

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