GSK 2830371

Cat. No.: HY-15832

CAS No.: 1404456-53-6

Molecular Formula: $C_{23}H_{29}ClN_4O_2S$

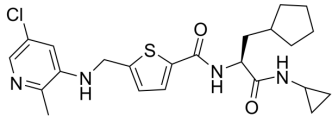
Molecular Weight: 461.02

Target: Phosphatase

Pathway: Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 51 mg/mL (110.62 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1691 mL	10.8455 mL	21.6910 mL
5 mM	0.4338 mL	2.1691 mL	4.3382 mL
10 mM	0.2169 mL	1.0846 mL	2.1691 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.42 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.42 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.42 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK 2830371 is a highly selective Wip1 phosphatase inhibitor with IC_{50} of 6 nM.

IC_{50} & Target

IC50: 6 nM (Wip1 phosphatase)[1]

In Vitro

GSK 2830371 potently inhibits Wip1 (2-420) dephosphorylation of FDP and the endogenous substrates phospho-p38 MAPK (T180) with IC_{50} values of 6 nM and 13 nM, respectively. In the PPM1D-amplified MCF7 breast carcinoma cells, treatment with

	GSK 2830371 (0.04, 0.11, 0.33, 1, 3, and 9 μM) increased phosphorylation of substrates in a concentration-dependent manner. Treatment of MX-1 and MCF7 cells (Wip1amplified, p53 wild type) with GSK 2830371 (0.001, 0.01, 0.1, 1, and 10 μM) causes concentration-dependent effects in cell growth assays[1]. GSK2830371 has a 50% growth inhibitory concentration (GI_{50}) of 2.65 μM±0.54 (SEM) in MCF-7 cells. Treatment of MCF-7 cells with 2.5μM GSK2830371 results in marked time-dependent degradation of both isoforms of WIP1 over 8 hours which correlated with p53 stabilisation and phospho-$p53^{Ser15}$ ($pp53^{Ser15}$) [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In a pharmacodynamic assay, orally administered GSK 2830371 increases phosphorylation of Chk2 (T68) and p53 (S15) and decreased Wip1protein concentrations in DOHH2 tumors. Following 14 d of oral dosing at 150 mg per kg body weight, BID (twice daily) and TID (thrice daily), GSK 2830371 inhibits the growth of DOHH2 tumor xenografts by 41% and 68%, respectively. Comparable tumor growth inhibition is observed in mice treated BID with either 75 or 150 mg per kg body weight. Greater tumor growth inhibition with the TID schedule is consistent with a short half-life of GSK 2830371 in mice and suggests that sustained inhibition of Wip1 may be required for maximal antitumor effect[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The primary in vitro Wip1 enzymatic assay measured fluorescence generated by Wip-1 (2-420) hydrolysis of fluorescein diphosphate (FDP). 50 μM FDP substrate is added with GSK 2830371 or DMSO at room temperature before addition of 10 nM Wip1 in assay buffer (50 mM TRIS, pH 7.5, 30 mM $MgCl_2$, 0.8 mM CHAPS, 0.05 mg/mL BSA). Fluorescent signal is detected on a Spectramax microplate reader (485/530 nm)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cells are seeded into 96 well plates at 200-400 cells per well and treated with GSK 2830371 dilution series on day 1. After 7 d, we used the CellTiter-Glo cell viability assay to determine effects on cell growth. Luminescent signal is detected on an EnVision 2104. For clonogenic assays, cells are seeded in 12-well tissue culture plates at 2,000 cells per well. Cells are treated with a compound dilution series on day 1 and again on day 7. After 14 d, cells are washed with 1× PBS, stained with 1 mL of Coomassie Brilliant Blue R-250, and colonies are quantitated with the Optomax Sorcerer colony counter[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female SCID mice are subcutaneously inoculated with $1×10^7$ DOHH2 cells and tumor growth is monitored with electronic calipers. When tumors reached 100-200 mm^3, animals are treated orally twice (BID) or thrice (TID) daily with vehicle (2% DMSO and 40% Captisol, pH 4.0) or GSK 2830371. For efficacy studies, eight mice per group are administered with GSK 2830371 at 75 or 150 mg per kg body weight BID or 150 mg per kg body weight TID. Tumor growth inhibition (% difference in tumor growth compared to control) is calculated when tumors for vehicle-control mice exceeded 1,000 mm^3 (day 11). For pharmacodynamic biomarker analysis, DOHH2 tumors from three mice are harvested 2 or 4 h after final dose following 14 d of treatment with either vehicle or GSK 2830371 at 75 or 150 mg per kg body weight, BID; tumors are frozen in liquid nitrogen for subsequent lysis and western blot analysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2022 Feb 1;13(1):604.
- Nat Commun. 2018 Sep 25;9(1):3923.
- Nucleic Acids Res. 2023 Jan 18;gkac1269.
- Cell Death Dis. 2019 Oct 28;10(11):818.

- Mol Oncol. 2023 Apr 17.

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REFERENCES

[1]. Gilmartin AG, et al. Allosteric Wip1 phosphatase inhibition through flap-subdomain interaction. Nat Chem Biol. 2014 Mar;10(3):181-7.

[2]. Esfandiari A, et al. Chemical Inhibition of Wild-Type p53-Induced Phosphatase 1 (WIP1/PPM1D) by GSK2830371 Potentiates the Sensitivity to MDM2 Inhibitors in a p53-Dependent Manner. Mol Cancer Ther. 2016 Mar;15(3):379-91.

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