GW843682X

Cat. No.: HY-11003

CAS No.: 660868-91-7

Molecular Formula: $C_{22}H_{18}F_3N_3O_4S$

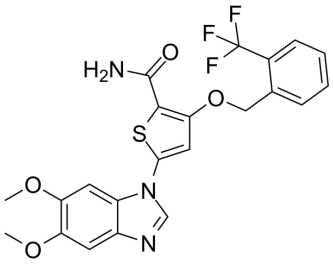
Molecular Weight: 477

Target: Polo-like Kinase (PLK)

Pathway: Cell Cycle/DNA Damage

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 : 33.33 mg/mL (69.87 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0964 mL	10.4822 mL	20.9644 mL
5 mM	0.4193 mL	2.0964 mL	4.1929 mL
10 mM	0.2096 mL	1.0482 mL	2.0964 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 (5.24 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.24 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GW843682X is a selective, ATP-competitive inhibitor of PLK1 and PLK3, with IC_{50}s of 2.2 nM and 9.1 nM, respectively, and is also >100-fold selective against -30 other kinases.

IC_{50} & Target

PLK1 2.2 nM (IC_{50})	PLK3 9.1 nM (IC_{50})	PDGFR1β 160 nM (IC_{50})	VEGFR2 360 nM (IC_{50})
Aurora A 4800 nM (IC_{50})	CDK2/cyclin A 7600 nM (IC_{50})		

In Vitro

GW843682X (compound 1) is effective on inhibition of growth of tumor cells, with IC_{50}s of 0.41, 0.57, 0.11, 0.38, and 0.70 μM

for A549, BT474, HeLa, H460 and HCT116 cell lines. GW843682X dose-dependently inhibits PLK1 phosphorylation of Ser15-p53, with an IC_{50} of 0.14 μM. GW843682X (3 μM) causes a strong G2-M arres in HDF cells and H460 cells after treatment for 24, 48, and 72 h. GW843682X (5 μM) leads to apoptosis in H460 cells instead of HDF cells[1]. GW843682X inhibits proliferation of U937 cells with an EC_{50} of 120 nM. GW843682X (500 nM) in combination with 5 μM VP-16 suppresses 50% of entry into mitosis in U937 cells[2]. GW843682X (0.06-1 μM) has inhibitory activities against proliferation of acute leukemia cells, and potentiates the anti-proliferative activity of vincristine. Moreover, GW843682X (0.1-1 μM) induces apoptosis of leukemia cells in a dose- and time-dependent manner. GW843682X (0.5-1 μM) dephosphorylates Bcl-xl in leukemia cells[3].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

PLK1 and PLK3 proteins are prepared from baculovirus-infected Trichoplusia ni cells. Enzyme activity for PLK1 and PLK3 is determined as follows. All measurements are obtained under conditions where signal production increased linearly with time and enzyme. Test compounds are added to white 384-well assay plates (0.1 μL for 10 μL and some 20 μL assays, 1 μL for some 20 μL assays) at variable known concentrations in 100% DMSO. DMSO (1-5% final) and EDTA (65 mM) are used as controls. Reaction Mix containes the following components at 22°C: 25 mM HEPES (pH 7.2); 15 mM $MgCl_2$; 1 μM ATP; 0.05 μ Ci/well [γ-^{33}P]ATP (10 Ci/mmol); 1 μM substrate peptide (Biotin-Ahx-SFNDTLDFD); 0.15 mg/mL bovine serum albumin; 1 mM DTT; and 2 nM PLK1 kinase domain or 5 nM full-length PLK3. Reaction Mix (10 or 20 μL) is quickly added to each well immediately following addition of enzyme via automated liquid handlers and incubated for 1 to 1.5 h at 22°C. The 20 μL enzymatic reactions are stopped with 50 μL of stop mix [50 mM EDTA, 4.0 mg/mL streptavidin SPA beads in Dulbecco's PBS (without Mg^{2+} and Ca^{2+}), 50 μM ATP] per well. The 10 μL reactions are stopped with 10 μL of stop mix [50 mM EDTA, 3.0 mg/mL streptavidin-coupled SPA Imaging Beadsin Dulbecco's PBS (without Mg^{2+} and Ca^{2+}), 50 μM ATP] per well. Plates are sealed, spun at 500 × g for 1 min or settled overnight, and counted in Packard TopCount for 30 s/well or imaged with a Viewlux imager. Signal above background (EDTA controls) is converted to percent inhibition relative to that obtained in control (DMSO-only) wells[1].

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Cell Assay [1]

Assays are carried out and data analyzed. In these assays, H460 cells are plated at a density of 2,000 per well, HDF cells are plated at 5,000 per well, and the drug-resistant cell line MES-SA/DX5 and its sensitive parent line MES-SA are plated at 7,000 and 6,000 per well, respectively, in a 96-well plate. These densities allowed vehicle controls to grow logarithmically during the course of the 3-day assay. All cells are exposed to 3-fold dilutions of the compound (30-0.00152 μM) in low-glucose DMEM containing 5% FBS, 50 μg/mL gentamicin, and 0.3% (v/v) DMSO (HDF cells); RPMI 1640 containing 5% FBS, 50 μg/mL gentamicin, and 0.3% (v/v) DMSO (H460); or McCoy's 5A containing 5% FBS, 50 μg/mL gentamicin, and 0.3% (v/v) DMSO (MES-SA and MES-SA/DX5)[1].

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CUSTOMER VALIDATION

- Cell Rep. 2021 Jun 8;35(10):109225.
- Advanced Therapeutics. 10 September 2022.
- Sci Rep. 2017 Aug 17;7(1):8629.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Lansing TJ, et al. In vitro biological activity of a novel small-molecule inhibitor of polo-like kinase 1. Mol Cancer Ther. 2007 Feb;6(2):450-9. Epub 2007 Jan 31.

[2]. Didier C, et al. Evaluation of Polo-like Kinase 1 inhibition on the G2/M checkpoint in Acute Myelocytic Leukaemia. Eur J Pharmacol. 2008 Sep 4;591(1-3):102-5.

[3]. Ikezoe T, et al. A novel treatment strategy targeting polo-like kinase 1 in hematological malignancies. Leukemia. 2009 Sep;23(9):1564-76.

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