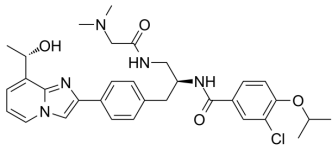
GSK-923295

Cat. No.:	HY-10299
CAS No.:	1088965-37-0
Molecular Formula:	$C_{32}H_{38}ClN_5O_4$
Molecular Weight:	592.13
Target:	Kinesin; Apoptosis
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton; Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 30 mg/mL (50.66 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.6888 mL	8.4441 mL	16.8882 mL
5 mM	0.3378 mL	1.6888 mL	3.3776 mL
10 mM	0.1689 mL	0.8444 mL	1.6888 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: ≥ 3 mg/mL (5.07 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 3 mg/mL (5.07 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (5.07 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK-923295 is a special, allosteric inhibitor of centromere-associated protein-E (CENP-E) kinesin motor ATPase activity, with K_i of 3.2±0.2 nM and 1.6± 0.1 nM for human and canine, respectively.

IC_{50} & Target

CENP-E
1.6 nM (Ki, Canine CENP-E)

In Vitro

GSK-923295 (GSK923295) is a first-in-class, specific, allosteric inhibitor of CENP-E kinesin motor function. GSK923295 is

	uncompetitive with both ATP and MT, inhibiting CENP-E MT-stimulated ATPase activity with a K_i of 3.2±0.2 nM and 1.6±0.1 nM for human and canine, respectively. GSK923295 inhibits release of inorganic phosphate and stabilized CENP-E motor domain interaction with microtubules[1]. GSK923295 has broad growth inhibitory activity in a panel of 237 cancer cell lines and produces significant tumor growth-delay in 8 of the 11 mouse xenograft tumor models with IC_{50}s of 17.2 nM, 55.6 nM, 42 nM, and 51.9 nM for SW48, RKO (BRAF mutant), SW620 (KRAS mutant), and HCT116 (KRAS mutant), respectively[2]. GSK923295 is a potent and selective small molecule inhibitor of human CENPE with a K_i of 3.2 nM. GSK923295 demonstrates broad efficacy against a panel of 19 human neuroblastoma derived cell lines with an average growth IC_{50} of 41 nM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Xenografts of mice treated with GSK-923295 (GSK923295) shows significant tumor growth delay compared to the control arm (NB-EBc1 $p<0.0001$; NB-1643 $p=0.018$; NB-1691 $p=0.0018$)[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cell-growth inhibition assays are performed by MDS in 384-well plates, and DNA content of fixed cells stained with DAPI using an Incell 1000 (GE) is analyzed. DNA content is determined 24 h after seeding (T_0) and after exposure to varying concentrations of GSK-923295 (0.01 nM, 0.1 nM, 1 nM, 10 nM, 100 nM, 1 μM, 10 μM, and 100 μM) for an additional 72 h (T_{72}). All T_{72} measurements are normalized to T_0. Curves are analyzed using the XLfit curve-fitting tool to determine the concentration of GSK923295 yielding 50% growth inhibition relative to T_0 and Y_{max} values (GI_{50})[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Mice[3] CB17 scid mice are used to propagate subcutaneously implanted neuroblastoma tumors. Tumor diameters are measured using calipers. Tumor volumes are calculated. Once tumor volume exceeds 200 mm^3, mice are randomized (n=10 per arm) to receive either GSK923295 125 mg/kg IP or vehicle (96% acidified water, 2% DMAC, 2% CREM) for a total of 6 doses using a 3 days on, 4 days off, 3 days on regimen. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2015 May 15;348(6236):799-803.
- Science. 2014 Oct 10;346(6206):244-7.
- Nat Cell Biol. 2015 Sep;17(9):1134-44.
- Nat Cell Biol. 2014 Dec;16(12):1249-56.
- Nat Cell Biol. 2012 Feb 5;14(3):295-303.

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REFERENCES

[1]. Wood KW, et al. Antitumor activity of an allosteric inhibitor of centromere-associated protein-E. Proc Natl Acad Sci U S A. 2010 Mar 30;107(13):5839-44.

[2]. Mayes PA, et al. Mitogen-activated protein kinase (MEK/ERK) inhibition sensitizes cancer cells to centromere-associated protein E (CENP-E) inhibition. Int J Cancer. 2013 Feb 1;132(3):E149-57.

[3]. Balamuth NJ, et al. Serial transcriptome analysis and cross-species integration identifies centromere-associated protein E as a novel neuroblastoma target. Cancer Res. 2010 Apr 1;70(7):2749-58.

Caution: Product has not been fully validated for medical applications. For research use only.

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