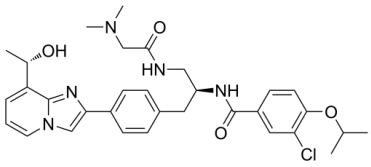
Data Sheet

Product Name:	GSK-923295
Cat. No.:	CS-0056
CAS No.:	1088965-37-0
Molecular Formula:	$C_{32}H_{38}ClN_5O_4$
Molecular Weight:	592.13
Target:	Apoptosis; Kinesin
Pathway:	Apoptosis; Cell Cycle/DNA Damage; Cytoskeleton
Solubility:	DMSO : 30 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: Ki: 3.2 nM (human CENP-E), 1.6 nM (canine CENP-E)[1] ***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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: GSK-923295 (GSK923295) is dissolved in DMSO and stored, and then diluted with appropriate media before use[1].[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]. **Animal Administration:** GSK-923295 (GSK923295) is prepared in 96% acidified water, 2% DMAC, and 2% CREM (Mice)[3].[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.

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.

CAIndexNames:

Benzamide, 3-chloro-N-[(1S)-2-[[2-(dimethylamino)acetyl]amino]-1-[[4-[8-[(1S)-1-hydroxyethyl]imidazo[1,2-a]pyridin-2-yl]phenyl]methyl]ethyl]-4-(1-methylethoxy)-

SMILES:

O=C(N[C@@H](CC1=CC=C(C2=CN3C(C([C@@H](O)C)=CC=C3)=N2)C=C1)CNC(CN(C)C)=O)C4=CC(Cl)=C(C=C4)OC(C)C

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