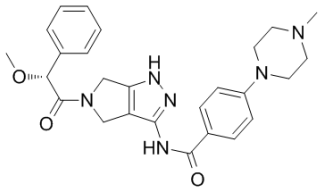
Danusertib

Cat. No.:	HY-10179
CAS No.:	827318-97-8
Molecular Formula:	$C_{26}H_{30}N_6O_3$
Molecular Weight:	474.55
Target:	Aurora Kinase; Autophagy
Pathway:	Cell Cycle/DNA Damage; Epigenetics; Autophagy
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 : 50 mg/mL (105.36 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1073 mL	10.5363 mL	21.0726 mL
	5 mM	0.4215 mL	2.1073 mL	4.2145 mL
	10 mM	0.2107 mL	1.0536 mL	2.1073 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.27 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Danusertib is a pyrrolo-pyrazole and aurora kinase inhibitor with IC_{50} of 13, 79, and 61 nM for Aurora A, B, and C, respectively.

IC_{50} & Target

Aurora A	Aurora B	Aurora C
13 nM (IC_{50})	79 nM (IC_{50})	61 nM (IC_{50})

In Vitro

Danusertib (0.01 to 50 μM) significantly decreases viability of C13 and A2780cp cells. The IC_{50}s are 10.40 and 1.83 μM for C13 cells, and 19.89 and 3.88 μM for A2780cp cells after 24- and 48-h treatment. Danusertib induces cell cycle arrest in G2/M phase in C13 and A2780cp cells. Danusertib treatment results in a marked increase in the percentage of cells arrested in G2/M phase and an accumulation of polyploidy in C13 and A2780cp cells. Danusertib demotes the expression of CDK1/CDC2

	and cyclin B1 but promotes the expression of p21 Waf1/Cip1, p27 Kip1, and p53. Danusertib induces autophagy in C13 and A2780cp cells with the involvement of PI3K/Akt/mTOR signaling pathway[1]. PHA-739358 strongly inhibits proliferation of all leukemic cell lines tested, with IC_{50} values ranging from 0.05 μM to 3.06 μM. PHA-739358 induces antiproliferative effects in BaF3-p210 cells, including IM-resistant M351T, E255K, and T315I mutants. PHA-739358 (5 μM) reduces phosphorylation of CrkL in BaF3-p210 wt cells and IM-resistant mutants[2]. Danusertibsertib leads to cell-cycle arrest and completely inhibits cell proliferation of the GEP-NET cells in vitro[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PHA-739358 (15 mg/kg twice a day, i.p.) and IM are well tolerated, and significantly inhibit proliferation of K562 cells andvirtually suppressed tumor growth during the 10-day treatment period[2]. In a subcutaneous murine xenograft model, danusertibsertib (2×15 mg/kg/d, i.p.) significantly reduces tumor growth in vivo compared with controls or mice treated with streptozotocine/5-fluorouracil[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	The MTT assay is performed to examine the effect of danusertib on the viability of C13 and A2780cp cells. Briefly, cells are seeded in 96-well culture plates at a density of 8×10^3 cells/well. After cells are attached, the cells are treated with danusertib at different concentrations (0.01-50 μM). The control cells receive the vehicle only. After 24-h incubation, 10 μL MTT (5 g/L) is added to each well and cultured for another 4 h. Then, the media is carefully aspirated and 100 μL DMSO is added. The absorbance at the 450 nm wavelength is measured with a Synergy H4 Hybrid microplate reader. The IC_{50} values are determined using the relative viability over danusertib concentration curve using GraphPad Prism 6.0. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	To evaluate the efficacy and toxicity of PHA-739358 in vivo, a subcutaneous animal model for CML is used; 5×10^7 K562 cells are injected into the flanks of female SCID mice and tumor growth is monitored daily by palpation. On day 7, when tumors reach an estimated weight of 100 to 150 mg, animals are assigned to 3 experimental groups by random selection and receive the following treatment for a period of 10 days: group 1, control, vehicle solution (7 mice); group 2, PHA-739358 twice a day intraperitoneally at a dose of 15 mg/kg (7 mice); and group 3, IM twice a day per os at 100 mg/kg. Tumor growth is assessed by caliper, and tumor weight is calculated according to the following formula: Tumor weight=[length (mm) × $width^2$ (mm)]/2. Toxicity is monitored by changes in body weight and vitality of the animals. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Mol Cancer Ther. 2020 Aug;19(8):1751-1760.
- Patent. US20180263995A1.
- Technical University of Munich. 24.01.2018.

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REFERENCES

[1]. Zi D, et al. Danusertib Induces Apoptosis, Cell Cycle Arrest, and Autophagy but Inhibits Epithelial to Mesenchymal Transition Involving PI3K/Akt/mTOR Signaling Pathway in Human Ovarian Cancer Cells. Int J Mol Sci. 2015 Nov 13;16(11):27228-51.

[2]. Gontarewicz A, et al. Simultaneous targeting of Aurora kinases and Bcr-Abl kinase by the small molecule inhibitor PHA-739358 is effective against imatinib-resistant

BCR-ABL mutations including T315I. Blood. 2008 Apr 15;111(8):4355-64.

[3]. Fraedrich K, et al. Targeting Aurora Kinases with Danusertib (PHA-739358) Inhibits Growth of Liver Metastases from Gastroenteropancreatic Neuroendocrine Tumors in an Orthotopic Xenograft Model. Clin Cancer Res. 2012 Sep 1;18(17):4621-32. Epub 2012 Jul 2.

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

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