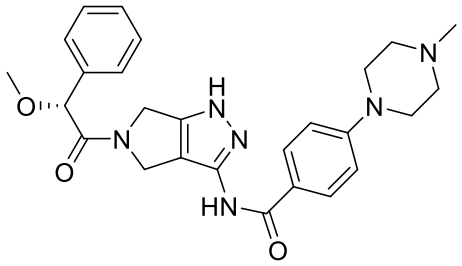
Product data sheet

MedKoo Cat#: 200846 Name: Danusertib CAS#: 827318-97-8 Chemical Formula: $C_{26}H_{30}N_6O_3$ Exact Mass: 474.23794 Molecular Weight: 474.55	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

Danusertib, also known as PHA-739358, is a small-molecule 3-aminopyrazole derivative with potential antineoplastic activity. Aurora kinase inhibitor PHA-739358 binds to and inhibits the Aurora kinases, which may result in cell growth arrest and apoptosis in tumor cells in which Aurora kinases are overexpressed. This agent may preferentially bind to and inhibit Aurora B kinase. Aurora kinases, a family of serine-threonine kinases, are important regulators of cellular proliferation and division.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	55.0	115.90

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.11 mL	10.54 mL	21.07 mL
5 mM	0.42 mL	2.11 mL	4.21 mL
10 mM	0.21 mL	1.05 mL	2.11 mL
50 mM	0.04 mL	0.21 mL	0.42 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Yuan CX, Zhou ZW, Yang YX, He ZX, Zhang X, Wang D, Yang T, Pan SY, Chen XW, Zhou SF. Danusertib, a potent pan-Aurora kinase and ABL kinase inhibitor, induces cell cycle arrest and programmed cell death and inhibits epithelial to mesenchymal transition involving the PI3K/Akt/mTOR-mediated signaling pathway in human gastric cancer AGS and NCI-N78 cells. Drug Des Devel Ther. 2015 Mar 2;9:1293-318. doi: 10.2147/DDDT.S74964. PMID: 25767376; PMCID: PMC4354435.
2. Zi D, Zhou ZW, Yang YJ, Huang L, Zhou ZL, He SM, He ZX, Zhou SF. 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. doi: 10.3390/ijms161126018. PMID: 26580601; PMCID: PMC4661876.

In vivo study

1. Gavriilidis P, Poutahidis T, Giakoustidis A, Makedou K, Angelopoulou K, Hardas A, Andreani P, Zacharioudaki A, Saridis G, Gargavanis A, Louri E, Antoniadis N, Karampela E, Psychalakis N, Michalopoulos A, Papalois A, Iliadis S, Mudan S, Azoulay D, Giakoustidis D. Targeting hepatocarcinogenesis model in C56BL6 mice with pan-aurora kinase inhibitor Danusertib. J Cancer. 2018 Feb 27;9(5):914-922. doi: 10.7150/jca.22329. PMID: 29581770; PMCID: PMC5868156.
2. Fraedrich K, Schrader J, Ittrich H, Keller G, Gontarewicz A, Matzat V, Kromminga A, Pace A, Moll J, Bläker M, Lohse AW, Hörsch D, Brümmendorf TH, Benten D. 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. doi: 10.1158/1078-0432.CCR-11-2968. Epub 2012 Jul 2. PMID: 22753592.

7. Bioactivity

Biological target:

Danusertib is a pyrrolo-pyrazole and aurora kinase inhibitor with IC50 of 13, 79, and 61 nM for Aurora A, B, and C, respectively.

In vitro activity

After finding that danusertib had a marked inducing effect on cell cycle arrest in G2/M phase in AGS and NCI-N78 cells, the expression level of key regulators responsible for G2 to M phase checkpoint was futher examined using the Western blotting assay to explore the possible mechanisms for danusertib-induced cell cycle arrest in both cell lines. As shown in Figure 4A and B, treatment with danusertib significantly inhibited expression of positive regulators but enhanced the negative regulators responsible for the G2 to M phase transition. Incubating AGS cells with danusertib 0.1 and 0.5 μM for 24 hours led to a 31% and 46% decrease in CDC2 expression and to a 51% and 53% reduction in cyclin B1 expression, respectively (Figure 4A and B). Similarly, treating NCI-N78 cells with 0.5 μM danusertib resulted in a 45% decrease in expression of CDC2. There was also a 75% and 70% reduction in expression of cyclin B1 when NCI-N78 cells were treated with danusertib 0.1 and 0.5 μM for 24 hours, respectively (Figure 4A and B).

Reference: Drug Des Devel Ther. 2015; 9: 1293–1318. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4354435/

In vivo activity

Treatment of tumor-bearing mice with danusertib at a dose of 2 × 15 mg/kg/d decreased growth of BON1 and QGP xenografts (Fig. 3A and B). BON1 tumor growth was significantly inhibited from day 4 ($P < 0.001$) until the end of the experiment ($P < 0.001$). The mean absolute tumor volume was reduced by 88.2%, and the mean percental tumor growth was also reduced by 88.2%, compared with vehicle-treated controls (Fig. 3A, Table 2). In mice with QGP xenografts, treatment with danusertib led to a virtual shrinkage of QGP tumors from day 4 ($P < 0.001$), until the end of the experiment ($P < 0.001$). The final tumor volume was only 6.3 ± 8.2% of the original tumor volume (Fig. 3B, Table 2). Mean absolute and percental tumor growth in danusertib-treated mice was reduced by 98.4% and 98.6%, respectively, compared with vehicle-treated controls. When compared with treatment with streptozotocine/5-fluoruracil (STZ/5-FU), which is a frequently used cytostatic therapy for GEP-NETs, the antiproliferative effect of danusertib was significantly higher from day 12 ($P < 0.001$), in both BON1 and QGP tumors (Fig. 3A and B, Table 2). Additionally, CgA levels were significantly lower in danusertib-treated animals (12.0 ± 12.4 nmol/L) compared with vehicle-treated controls ($P < 0.001$, $n = 9$) and mice treated with STZ/5-FU (32.0 ± 12.9 nmol/L, $P < 0.05$, $n = 6$; Fig. 3C).

Reference: Clin Cancer Res. 2012 Sep 1;18(17):4621-32. https://pubmed.ncbi.nlm.nih.gov/22753592/