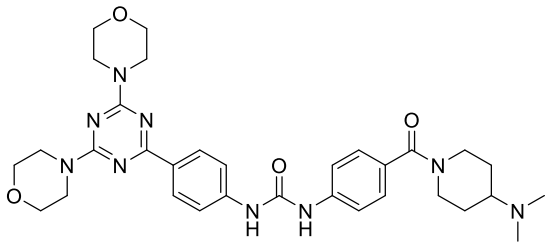
Product data sheet

MedKoo Cat#: 202255 Name: Gedatolisib CAS#: 1197160-78-3 Chemical Formula: $C_{32}H_{41}N_9O_4$ Exact Mass: 615.32815 Molecular Weight: 615.72	
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:

Gedatolisib, also known as PKI-587 and PF-05212384, is an agent targeting the phosphatidylinositol 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) in the PI3K/mTOR signaling pathway, with potential antineoplastic activity. Upon intravenous administration, PI3K/mTOR kinase inhibitor PKI-587 inhibits both PI3K and mTOR kinases, which may result in apoptosis and growth inhibition of cancer cells overexpressing PI3K/mTOR. Activation of the PI3K/mTOR pathway promotes cell growth, survival, and resistance to chemotherapy and radiotherapy; mTOR, a serine/threonine kinase downstream of PI3K, may also be activated independent of PI3K.

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	2.77	4.50
DMF	1.5	2.44
DMF:PBS (pH 7.2) (1:1)	0.5	0.81

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.62 mL	8.12 mL	16.24 mL
5 mM	0.32 mL	1.62 mL	3.25 mL
10 mM	0.16 mL	0.81 mL	1.62 mL
50 mM	0.03 mL	0.16 mL	0.32 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. Gazi M, Moharram SA, Marhäll A, Kazi JU. The dual specificity PI3K/mTOR inhibitor PKI-587 displays efficacy against T-cell acute lymphoblastic leukemia (T-ALL). Cancer Lett. 2017 Apr 28;392:9-16. doi: 10.1016/j.canlet.2017.01.035. Epub 2017 Feb 1. Erratum in: Cancer Lett. 2019 Oct 1;461:155. PMID: 28159681.
2. Freitag H, Christen F, Lewens F, Grass I, Briest F, Iwaszkiewicz S, Siegmund B, Grabowski P. Inhibition of mTOR's Catalytic Site by PKI-587 Is a Promising Therapeutic Option for Gastroenteropancreatic Neuroendocrine Tumor Disease. Neuroendocrinology. 2017;105(1):90-104. doi: 10.1159/000448843. Epub 2016 Aug 12. PMID: 27513674; PMCID: PMC5475233.

In vivo study

Product data sheet

1. Shor RE, Dai J, Lee SY, Pisarsky L, Matei I, Lucotti S, Lyden D, Bissell MJ, Ghajar CM. The PI3K/mTOR inhibitor Gedatolisib eliminates dormant breast cancer cells in organotypic culture, but fails to prevent metastasis in preclinical settings. Mol Oncol. 2021 May 31. doi: 10.1002/1878-0261.13031. Epub ahead of print. PMID: 34058066.
2. Mallon R, Feldberg LR, Lucas J, Chaudhary I, Dehnhardt C, Santos ED, Chen Z, dos Santos O, Ayral-Kaloustian S, Venkatesan A, Hollander I. Antitumor efficacy of PKI-587, a highly potent dual PI3K/mTOR kinase inhibitor. Clin Cancer Res. 2011 May 15;17(10):3193-203. doi: 10.1158/1078-0432.CCR-10-1694. Epub 2011 Feb 15. PMID: 21325073.

7. Bioactivity

Biological target:

Gedatolisib (PKI-587) is a dual inhibitor of PI3Kα, PI3Kγ, and mTOR with IC50s of 0.4 nM, 5.4 nM and 1.6 nM, respectively.

In vitro activity

In this study, two different gene expression datasets of relapsed patients also displayed a predominant enrichment of the PI3K/mTOR pathway. Using a panel of 88 different inhibitors which target several different components of this pathway, PKI-587 was found to be the most selective drug that induces apoptosis of T-ALL cell lines that are dependent on the activity of the PI3K/mTOR pathway. An important observation was made, that the inhibitor PKI-587 was effective even in the presence of micro-environmental factors. The use of conditioned medium from the bone marrow HS5 cells had very little or no effect on PKI-587-induced inhibition of cell growth. This is interesting since it has been suggested that the bone marrow microenvironment, presumably through cytokine production, helps to protect leukemic cells from drug-induced death and thereby contributes to therapy resistance. These findings provide a basis for the use of the dual specificity inhibitor PKI-587 as a promising drug for the treatment of T-ALL. These biological assays also suggest a strong ability of PKI-578 to block cell proliferation, colony formation and to induce apoptosis of T-ALL cell lines.

Reference: Cancer Lett. 2017 Apr 28;392:9-16. https://pubmed.ncbi.nlm.nih.gov/28159681/

In vivo activity

Gedatolisib alone did not yield an obvious advantage in decreasing or preventing metastatic disease ompared to vehicle-treated mice. Nor did Gedatolisib augment dose-dense AC therapy in a manner consistent with alleviation of disease burden (Fig. 3b-f). Vehicle treated mice had a roughly equivalent number of DTCs in the left lobe of the lung compared to mice treated with AC, Gedatolisib, or Gedatolisib + AC (Fig. 3b-c). T4-2 cells delivered to athymic nude mice via intracardiac injection tend to form metastases in their skull, brain and adrenal glands. Regimens containing dose-dense AC yielded a significant and substantial decrease in average luciferase signal 410 in the skull and adrenal glands (Fig. 3d-e). Signal in all other tissues assessed, including brain, was unaffected (Fig. 3e-f). On its own, Gedatolisib did result in a significant decrease in luciferase signal 412 emitted from the kidneys and adrenal glands (Fig. 3e). However, priming with Gedatolisib did not enhance the efficacy of AC. In fact, the two mice with the highest brain luciferase signal in this study received the PI3K/mTOR inhibitor in addition to dose-dense AC regimen (Fig. 3e). These data demonstrate that Gedatolisib, alone or in combination with AC, does not reliably or significantly decrease metastatic burden or eradicate DTCs in a preclinical model of TNBC metastasis. On the contrary, dose-dense chemotherapy offers the best treatment option across metrics measured, and addition of Gedatolisib skews some of these metrics in the wrong direction.

Reference: Mol Oncol. 2021 May 31. https://pubmed.ncbi.nlm.nih.gov/34058066/