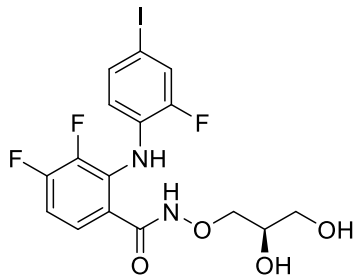
Product data sheet

MedKoo Cat#: 202172 Name: Mirdametinib CAS#: 391210-10-9 Chemical Formula: $C_{16}H_{14}F_3IN_2O_4$ Exact Mass: 481.99503 Molecular Weight: 482.19	
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:
Mirdametinib, also known as PD-0325901, is a potent bioavailable and selective MEK inhibitor, which targets mitogen-activated protein kinase kinase (MAPK/ERK kinase or MEK) with potential antineoplastic activity. MEK inhibitor PD325901, a derivative of MEK inhibitor CI-1040, selectively binds to and inhibits MEK, which may result in the inhibition of the phosphorylation and activation of MAPK/ERK and the inhibition of tumor cell proliferation. The dual specific threonine/tyrosine kinase MEK is a key component of the RAS/RAF/MEK/ERK signaling pathway that is frequently activated in human tumors.

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	80.0	165.91
Ethanol	80.0	165.91

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.07 mL	10.37 mL	20.74 mL
5 mM	0.41 mL	2.07 mL	4.15 mL
10 mM	0.21 mL	1.04 mL	2.07 mL
50 mM	0.04 mL	0.21 mL	0.41 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. Henderson YC, Chen Y, Frederick MJ, Lai SY, Clayman GL. MEK inhibitor PD0325901 significantly reduces the growth of papillary thyroid carcinoma cells in vitro and in vivo. Mol Cancer Ther. 2010 Jul;9(7):1968-76. doi: 10.1158/1535-7163.MCT-10-0062. Epub 2010 Jun 29. PMID: 20587665; PMCID: PMC2935263.

2. Barrett SD, Bridges AJ, Dudley DT, Saltiel AR, Fergus JH, Flamme CM, Delaney AM, Kaufman M, LePage S, Leopold WR, Przybranowski SA, Sebolt-Leopold J, Van Becelaere K, Doherty AM, Kennedy RM, Marston D, Howard WA Jr, Smith Y, Warmus JS, Tecle H. The discovery of the benzhydroxamate MEK inhibitors CI-1040 and PD 0325901. Bioorg Med Chem Lett. 2008 Dec 15;18(24):6501-4. doi: 10.1016/j.bmcl.2008.10.054. Epub 2008 Oct 15. PMID: 18952427.

In vivo study

1. Henderson YC, Chen Y, Frederick MJ, Lai SY, Clayman GL. MEK inhibitor PD0325901 significantly reduces the growth of papillary thyroid carcinoma cells in vitro and in vivo. Mol Cancer Ther. 2010 Jul;9(7):1968-76. doi: 10.1158/1535-7163.MCT-10-0062. Epub 2010 Jun 29. PMID: 20587665; PMCID: PMC2935263.

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7. Bioactivity

Biological target:

Mirdametinib (PD0325901) is a selective and non ATP-competitive MEK inhibitor with IC50 of 0.33 nM in cell-free assays, roughly 500-fold more potent than CI-1040 on phosphorylation of ERK1 and ERK2.

In vitro activity

To assess the effects of PD0325901 on PTC cell growth, the GI50 was determined in PTC cell lines (TPC-1 and K2). Cells were treated in vitro with serial dilution of the PD0325901 ranging from 100 nmol/L to 0.0064 nmol/L. After 2 days of incubation with varying concentrations of PD0325901, cell growth was determined by MTT. The GI50 was 11 nmol/L for TPC-1 cells and 6.3 nmol/L for K2 cells, as determined by Prism software (Fig. 1A). After determining the GI50 of PD0325901 in PTC cells, PTC cells were treated with PD0325901 at three different concentrations (100, 10, or 1 nmol/L) for 4 days. After 4 days of treatment, results of the MTT assay indicated that PD0325901 suppressed the cell growth by 80% ($P < 0.0001$), 75% ($P < 0.0001$), and 27% ($P = 0.0015$) in K2 cells, and by 58% ($P < 0.0001$), 40% ($P = 0.0002$), and 26% ($P = 0.0001$) in TPC-1 cells, respectively (Fig. 1B). Both K2 and TPC-1 cells showed dose-dependent growth inhibition with PD0325901. These data showed that PD0325901 significantly inhibited the growth of PTC cells harboring a BRAF mutation at very low concentration (10 nmol/L) and only moderately reduced the growth of the PTC cells carrying the RET/PTC1 rearrangement at the same concentration.

Reference: Mol Cancer Ther. 2010 Jul;9(7):1968-76. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/20587665/

In vivo activity

The inhibitory effects of PD0325901 were evaluated in vivo using a murine orthotopic xenograft model. PTC cells expressing luciferase were inoculated in situ into the right thyroid lobe of Ncr-nu/nu mice. A group of 10 mice was randomly selected after Xenogen luciferase bioimaging and used for treatment with vehicle, and 14 to 16 mice were used for the PD0325901 treatment group. One week after inoculation, PD0325901 was given to these mice (see Materials and Methods) for 3 weeks at 20 to 25 mg/kg. Tumor growth was monitored weekly by Xenogen luciferase bioimaging. Tumor sizes were measured and tumor volume was calculated if mice were sacrificed due to loss of 20% initial body weight or tumor burden. No tumors were detected by Xenogen in mice inoculated with K2 cells after 1 week of PD0325901 treatment, whereas mice treated with vehicle still showed intense luciferase expression (Fig. 3A). The treated mice remained tumor free during the 3-week treatment period (data not shown). At the end of 3 weeks, all mice inoculated with K2 and treated with vehicle were sacrificed with average tumor volume of 1,078.7 ± 285.3 mm3 (Fig. 3B). Tumor regression was apparent in 100% of mice harboring K2 tumors and treated with PD0325901, and therefore no mice in the treatment group died by 30 days due to tumor burden, whereas nearly 100% of mice treated with vehicle died within the same period (Fig. 3C). In mice inoculated with TPC-1 cells, the average tumor volume after 3 weeks of PD0325901 treatment was reduced by 58.3% (from 699 to 291.3 mm3; $P = 0.0004$) when compared with tumors from untreated (vehicle) mice (699 ± 241.8 mm3). In addition, the survival of the mice inoculated with TPC-1 cells was increased significantly compared with mice treated with vehicle (Fig. 3C). Median survival was 16 to 18 days in vehicle-treated animals and 30 to 33 days in PD0325901-treated mice ($P = 0.00124$). Similar to CI-1040, the solubility of PD0325901 remains an issue. The solubility of PD0325901 at pH 7 is only at 0.39 mg/mL. The poor solubility of PD0325901 resulted in a high percentage of censored deaths in mice inoculated with K2 cells (47–93%; Fig. 3C), although necropsy of these mice showed that no tumor was present in the thyroid. These data showed that PD0325901 suppressed tumor growth completely in mice inoculated with PTC cells carrying a BRAF mutation (K2) and significantly decreased tumor growth in mice inoculated with PTC cells carrying the RET/PTC1 rearrangement (TPC-1).

Reference: Mol Cancer Ther. 2010 Jul;9(7):1968-76. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/20587665/