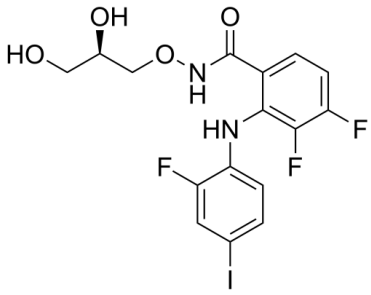
Data Sheet

Product Name:	Mirdametinib
Cat. No.:	CS-0062
CAS No.:	391210-10-9
Molecular Formula:	$C_{16}H_{14}F_3IN_2O_4$
Molecular Weight:	482.19
Target:	Apoptosis; Autophagy; MEK
Pathway:	Apoptosis; Autophagy; MAPK/ERK Pathway
Solubility:	DMSO : ≥ 56 mg/mL



BIOLOGICAL ACTIVITY:

Mirdametinib (PD0325901) is an orally active, selective and non-ATP-competitive **MEK** inhibitor with an **IC_{50}** of 0.33 nM. Mirdametinib exhibits a **K_i^{app}** of 1 nM against activated MEK1 and MEK2. Mirdametinib suppresses the expression of p-ERK1/2 and induces **apoptosis**. Mirdametinib has anti-cancer activity for a broad spectrum of human tumor xenografts[1][2][3]. ***In Vitro:***Mirdametinib (PD325901; 0.0064, 0.032, 0.16, 0.8, 4, 20, 100 nM; for 2 days) inhibits the growth of Papillary thyroid carcinomas (PTC) cell lines (TPC-1 cells and K2 cells) with GC_{50} of 11 nM and 6.3 nM, respectively[3].

Mirdametinib (100 nmol/L; for 4 days) induces apoptosis in K2 cells (top) or TPC-1 cells[3].

Mirdametinib (0.1, 1, 10, 100, 1000 nM; for 1 hour) suppresses the expression of p-ERK1/2 in K2 cells (top) or TPC-1 cells[3].

Mirdametinib prevents the growth of melanoma cell lines. Mirdametinib significantly prevents the the growth of PTC cells harboring a BRAF mutation at very low concentration (10 nM)[3].

In Vivo:Mirdametinib (25 mg/kg, p.o.) inhibits phosphorylation of ERK by more than 50% at 24 hours post-dosing. Mirdametinib (25 mg/kg/day; po) produces a 70% incidence of complete tumor responses (C26 model)[2].

Mirdametinib (20-25 mg/kg/day; oral gavage; for 3 weeks (5 consecutive days/week)) suppresses 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) in athymic Ncr-nu/nu mice at ages 6 to 8 weeks[3].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay:[1]Incorporation of ^{32}P into myelin basic protein (MBP) is assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) and a glutathione S-transferase protein containing p45MEK (GST-MEK). The assay solution contained 20 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 1 mM EGTA, 50 mM [gamma-^{32}P]ATP, 10 mg GST-MEK, 0.5 mg GST-MAPK and 40 mg MBP in a final volume of 100 mL. Reactions are stopped after 20 minutes by addition of trichloroacetic acid and filtered through a GF/C filter mat. ^{32}P retained on the filter mat is determined using a 1205 Betaplate. PD0325901 is assessed at various dose ranges in order to determine dose response curves. **Cell Assay:**Mirdametinib is dissolved in DMSO.[2]PTC cells (1×10^4) are seeded in 24-well plates with 1 mL of medium for 4 days in a 37°C incubator. MEK inhibitor PD0325901 at varying concentrations is added to the cells in triplicate on day 0. MTT dissolved in 0.8% NaCl solution at 5 mg/mL is added to each well (0.2 mL) on day 2 to test GC_{50} or every day for cell growth curves. The cells are incubated at 37°C for 3 hours with MTT. The liquid is then aspirated from the wells and discarded. Stained cells are dissolved in 0.5 mL of DMSO and their absorption at 570 nm is measured using a Synergy HT multidetection microplate reader. For GC_{50}, cell growth is calculated as $100\times(T-T_0)/(C-T_0)$, where T is the optical density of the wells treated with inhibitors after a 48-hour period, T_0 is the optical density at time zero, and C is the control optical density with DMSO only. **Animal Administration:**PD0325901 is dissolved in 80 mM citric

buffer.[2]Mice (10-14 per group) are anesthetized s.c. with a cocktail. K2 and TPC-1 cells stably infected with a retrovirus expressing luciferase (5×10^5 cells in 5 μL RPMI1640 medium) are inoculated into the thyroid gland, and the mice are monitored weekly for tumor growth by Xenogen using Living Image 3.0 software. One week after inoculation, PD0325901 is dissolved in 80 mM citric buffer (pH 7) by sonication and given to mice daily by oral gavage (20-25 mg/kg) for 3 weeks (5 consecutive days/week). Mice are sacrificed only due to tumor burden or loss of 20% of body weight. Tumor sizes are measured with calipers and tumor volume (V) is calculated by the formula (V=length×width×depth). Control mice are given 80 mM citric buffer (pH 7) alone. All in vivo experiments are done at least twice.

References:

[1]. Barrett SD, et al. The discovery of the benzhydroxamate MEK inhibitors CI-1040 and PD 0325901. Bioorg Med Chem Lett. 2008 Dec 15;18(24):6501-4.

[2]. Henderson YC, et al. 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.

[3]. Judith S. Sebolt-Leopold, et al. The biological profile of PD 0325901: A second generation analog of CI-1040 with improved pharmaceutical potential

CAIndexNames:

Benzamide, N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-

SMILES:

O=C(C1=CC=C(C(F)=C1NC2=CC=C(I)C=C2F)F)NOC[C@H](O)CO

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