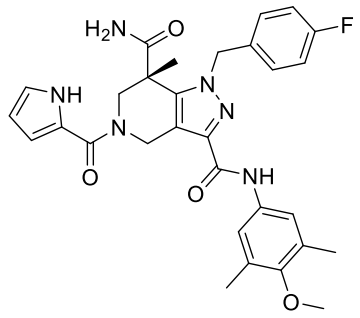
Product data sheet

MedKoo Cat#: 407369 Name: GSK864 CAS: 1816331-66-4 Chemical Formula: $C_{30}H_{31}FN_6O_4$ Exact Mass: 558.2391 Molecular Weight: 558.6144	
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:

GSK864 is a potent and selective inhibitor of mutant IDH1. GSK864 inhibits IDH1 mutants R132C/R132H/R132G with IC50 values of 9/15/17 nM, respectively, and is moderately selective over wild-type IDH1 and IDH2 mutants/wild-type. Treatment of R132C IDH1 mutant HT-1080 cells for 24 hours with GSK864 results in a dose-dependent reduction of 2-hydroxyglutarate (2-HG), which is not observed with GSK990, a structurally similar compound which is inactive as an IDH1 inhibitor. GSK864 has been shown to be selective in vitro for IDH1 over other classes of proteins (7TMs, ion channels, kinases) and chemoproteomic studies with GSK321, an analog of GSK864, confirm selective binding of IDH1 by this chemical series. GSK864 has a pharmacokinetic profile suitable for in vivo studies.

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
DMF	20.0	35.80
DMSO	60.0	107.41
Ethanol	20.0	35.80
Ethanol:PBS (pH 7.2) (1:1)	0.5	0.90

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.79 mL	8.95 mL	17.90 mL
5 mM	0.36 mL	1.79 mL	3.58 mL
10 mM	0.18 mL	0.90 mL	1.79 mL
50 mM	0.04 mL	0.18 mL	0.36 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. Mao MJ, Leonardi DE. Vascular-endothelial response to IDH1 mutant fibrosarcoma secretome and metabolite: implications on cancer microenvironment. Am J Cancer Res. 2019 Jan 1;9(1):122-133. PMID: 30755816; PMCID: PMC6356916.

2. Okoye-Okafor UC, Bartholdy B, Cartier J, Gao EN, Pietrak B, Rendina AR, Rominger C, Quinn C, Smallwood A, Wiggall KJ, Reif AJ, Schmidt SJ, Qi H, Zhao H, Joberty G, Faelth-Savitski M, Bantscheff M, Drewes G, Duraiswami C, Brady P, Groy A, Narayanagari SR, Antony-Debre I, Mitchell K, Wang HR, Kao YR, Christopeit M, Carvajal L, Barreyro L, Paietta E, Makishima H, Will B, Concha N, Adams ND, Schwartz B, McCabe MT, Maciejewski J, Verma A, Steidl U. New IDH1 mutant inhibitors for treatment of acute myeloid leukemia. Nat Chem Biol. 2015 Nov;11(11):878-86. doi: 10.1038/nchembio.1930. Epub 2015 Oct 5. PMID: 26436839; PMCID: PMC5155016.

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In vivo study

1. Okoye-Okafor UC, Bartholdy B, Cartier J, Gao EN, Pietrak B, Rendina AR, Rominger C, Quinn C, Smallwood A, Wiggall KJ, Reif AJ, Schmidt SJ, Qi H, Zhao H, Joberty G, Faelth-Savitski M, Bantscheff M, Drewes G, Duraiswami C, Brady P, Groy A, Narayanagari SR, Antony-Debre I, Mitchell K, Wang HR, Kao YR, Christopeit M, Carvajal L, Barreyro L, Paietta E, Makishima H, Will B, Concha N, Adams ND, Schwartz B, McCabe MT, Maciejewski J, Verma A, Steidl U. New IDH1 mutant inhibitors for treatment of acute myeloid leukemia. Nat Chem Biol. 2015 Nov;11(11):878-86. doi: 10.1038/nchembio.1930. Epub 2015 Oct 5. PMID: 26436839; PMCID: PMC5155016.

7. Bioactivity

Biological target:

GSK864 is an isocitrate dehydrogenase 1 (IDH1) mutant inhibitor; inhibits IDH1 mutants R132C, R132H, and R132G with IC_{50} values of 8.8, 15.2 and 16.6 nM.

In vitro activity

Indeed, GSK864 attenuated the proliferation of both fibrosarcoma cells and normal fibroblasts with a similar trend (Figure 5B). Despite their different proliferation rates, GSK864 significantly reduced the proliferation of fibrosarcoma cells and normal fibroblasts at doses of 0.8, 1.6 and 2 μmol, relative to control and at doses of 0.2 and 0.4 μmol (Figure 5B). These findings suggest that GSK864 not only attenuated the proliferation of IDH1 mutant cancer cells, but also fibroblasts such as those found in cancer stroma. Thus, GSK864 attenuation of vascular-endothelial tube formation (Figure 3), reversable by IDH mutant 2HG to which GSK864 inhibits, may represent a novel me-chanism by which GSK864 or other small molecules may be harnessed to target cancer stromal cells.

Reference: Am J Cancer Res. 2019 Jan 1;9(1):122-133. https://pubmed.ncbi.nlm.nih.gov/30755816/

In vivo activity

IDH1 WT or mutant AML patient BM cells were transplanted into sublethally irradiated NSG mice (Supplementary Fig. 4a), and comparable levels of AML engraftment were observed in BM aspirates 3 weeks after transplantation, and prior to treatment with either vehicle or 150 mg/kg GSK864. Following treatment this study observed a decrease in 2HG in IDH1-mutant AML cells of GSK321 treated mice (Supplementary Fig. 3f). After treatment with GSK864, this study observed a significant decrease in the percentage of blast cells (SSClow CD45low/+) and a relative increase in mature lymphoid and granulocytic/monocytic cells (Supplementary Fig. 4c).

Reference: Nat Chem Biol. 2015 Nov;11(11):878-86. https://pubmed.ncbi.nlm.nih.gov/26436839/