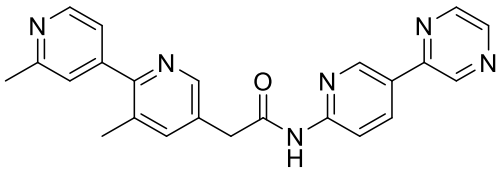
Product data sheet

MedKoo Cat#: 205851 Name: LGK974 CAS#: 1243244-14-5 (free base) Chemical Formula: $C_{23}H_{20}N_6O$ Exact Mass: 396.16986 Molecular Weight: 396.44	
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:

LGK974, also known as WNT974, is a selective and orally bioavailable porcupine (PORCN) inhibitor under development for the treatment of cancers that are driven by the Wnt pathway in a Wnt ligand-dependent manner. WNT974 binds to and inhibits PORCN in the endoplasmic reticulum (ER), which blocks post-translational acylation of Wnt ligands and inhibits their secretion. This prevents the activation of Wnt ligands, interferes with Wnt-mediated signaling, and inhibits cell growth in Wnt-driven tumors. Porcupine, a membrane-bound O-acyltransferase (MBOAT), is required for the palmitoylation of Wnt ligands, and plays a key role in Wnt ligand secretion and activity. Wnt signaling is dysregulated in a variety of cancers.

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	32	80.72

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.52 mL	12.61 mL	25.22 mL
5 mM	0.50 mL	2.52 mL	5.04 mL
10 mM	0.25 mL	1.26 mL	2.52 mL
50 mM	0.05 mL	0.25 mL	0.50 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. Liu J, Pan S, Hsieh MH, Ng N, Sun F, Wang T, Kasibhatla S, Schuller AG, Li AG, Cheng D, Li J, Tompkins C, Pferdekamper A, Steffy A, Cheng J, Kowal C, Phung V, Guo G, Wang Y, Graham MP, Flynn S, Brenner JC, Li C, Villarroel MC, Schultz PG, Wu X, McNamara P, Sellers WR, Petruzzelli L, Boral AL, Seidel HM, McLaughlin ME, Che J, Carey TE, Vanasse G, Harris JL. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. Proc Natl Acad Sci U S A. 2013 Dec 10;110(50):20224-9. doi: 10.1073/pnas.1314239110. Epub 2013 Nov 25. PMID: 24277854; PMCID: PMC3864356.

2. Jiang X, Hao HX, Growney JD, Woolfenden S, Bottiglio C, Ng N, Lu B, Hsieh MH, Bagdasarian L, Meyer R, Smith TR, Avello M, Charlat O, Xie Y, Porter JA, Pan S, Liu J, McLaughlin ME, Cong F. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. Proc Natl Acad Sci U S A. 2013 Jul 30;110(31):12649-54. doi: 10.1073/pnas.1307218110. Epub 2013 Jul 11. PMID: 23847203; PMCID: PMC3732970.

In vivo study

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1. Liu J, Pan S, Hsieh MH, Ng N, Sun F, Wang T, Kasibhatla S, Schuller AG, Li AG, Cheng D, Li J, Tompkins C, Pferdekamper A, Steffy A, Cheng J, Kowal C, Phung V, Guo G, Wang Y, Graham MP, Flynn S, Brenner JC, Li C, Villarroel MC, Schultz PG, Wu X, McNamara P, Sellers WR, Petruzzelli L, Boral AL, Seidel HM, McLaughlin ME, Che J, Carey TE, Vanasse G, Harris JL. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. Proc Natl Acad Sci U S A. 2013 Dec 10;110(50):20224-9. doi: 10.1073/pnas.1314239110. Epub 2013 Nov 25. PMID: 24277854; PMCID: PMC3864356.

2. Jiang X, Hao HX, Growney JD, Woolfenden S, Bottiglio C, Ng N, Lu B, Hsieh MH, Bagdasarian L, Meyer R, Smith TR, Avello M, Charlat O, Xie Y, Porter JA, Pan S, Liu J, McLaughlin ME, Cong F. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. Proc Natl Acad Sci U S A. 2013 Jul 30;110(31):12649-54. doi: 10.1073/pnas.1307218110. Epub 2013 Jul 11. PMID: 23847203; PMCID: PMC3732970.

7. Bioactivity

Biological target:

LGK-974 (NVP-LGK974, WNT974) is a potent and specific PORCN inhibitor, and inhibits Wnt signaling with IC50 of 0.4 nM in TM3 cells.

In vitro activity

Medicinal chemistry optimization of GNF-1331 was carried out to improve potency and pharmacokinetic properties. This effort led to the discovery of LGK974 (Fig. 1B), a highly specific and potent PORCN inhibitor. LGK974 effectively displaced [3H]-GNF-1331 with an IC50 of 1 nM in the PORCN radioligand binding assay (Fig. 1C and Fig. S1B). LGK974 also potently inhibited Wnt signaling in the aforementioned Wnt coculture assay with an IC50 of 0.4 nM (Fig. 1D). This inhibitory effect was rescued by the addition of exogenous Wnt3A CM (Fig. 1E). Additionally, LGK974 showed no major cytotoxicity in cells up to 20 μM (Fig. S1C). To further confirm the activity of LGK974 in blocking PORCN-dependent Wnt secretion, 293A cells were transfected with HA-tagged Wnt3A and treated with various doses of LGK974. As shown in Fig. 1F and Fig. S1D, LGK974 potently decreased levels of HA-Wnt3A in the supernatant with slightly increased levels of HA-Wnt3A in the cell lysate, suggesting that Wnt3A secretion was substantially inhibited by LGK974 in a dose-dependent manner. In Wnt-responsive cells, secreted Wnts cause phosphorylation of the Wnt coreceptor LRP6. In L-Wnt3A cells, a mouse cell line overexpressing Wnt3A, LGK974, strongly blocked Wnt-dependent phosphorylation of LRP6 (Fig. S1E).

Reference: Proc Natl Acad Sci U S A. 2013 Dec 10;110(50):20224-9. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24277854/

In vivo activity

In a murine MMTV-Wnt1 tumor model using s.c. implanted tumor fragments derived from MMTV-Wnt1 transgenic mice, LGK974 exhibited strong dose-dependent efficacy when administered daily (Fig. 2A). Briefly, changes in tumor volume for each of the treated (T) and control (C) groups were measured and used to calculate growth delay as expressed by the T/C ratio. A dose of 0.3 mg/kg LGK974 led to tumor growth delay (T/C: 26%), whereas a dose of 1 or 3 mg/kg induced very significant tumor regression (T/C: −47% or −63%, respectively) on day 13 of treatment. As shown in Fig. S2A, the regimen was well-tolerated without significant body weight loss in the mice. Similar efficacy was observed with LGK974 in a murine MMTV-Wnt3 model (Fig. S2B).

Reference: Proc Natl Acad Sci U S A. 2013 Dec 10;110(50):20224-9. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24277854/