LGK974

Cat. No.: HY-17545

CAS No.: 1243244-14-5

Molecular Formula: $C_{23}H_{20}N_6O$

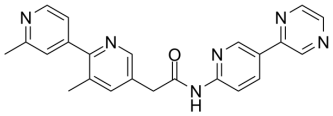
Molecular Weight: 396.44

Target: Porcupine

Pathway: Stem Cell/Wnt

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 32 mg/mL (80.72 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5224 mL	12.6122 mL	25.2245 mL
5 mM	0.5045 mL	2.5224 mL	5.0449 mL
10 mM	0.2522 mL	1.2612 mL	2.5224 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.31 mM); Suspended solution; Need ultrasonic and warming
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.31 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LGK974 (WNT974) is an orally bioavailable and specific Porcupine (PORCN) inhibitor with an IC_{50} of 0.1 nM[1].

IC_{50} & Target

Porcupine[1]

In Vitro

LGK974 effectively displaces [^{3}H]-GNF-1331 with an IC_{50} of 1 nM in the PORCN radioligand binding assay. LGK974 potently reduces Wnt-dependent AXIN2 mRNA levels in HN30 cells with an IC_{50} of 0.3 nM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

LGK974, a drug that targets Porcupine, a Wnt-specific acyltransferase. LGK974 potently inhibits Wnt signaling, has strong

	efficacy in rodent tumor models, and is well-tolerated. Toxicology studies are performed on nontumor bearing rats at 3 and 20 mg/kg. At the efficacious dose of 3 mg/kg per day for 14 d, LGK974 is well-tolerated without abnormal histopathological findings in Wnt-dependent tissues, including the intestine, stomach, and skin. When rats are administrated a very high dose of 20 mg/kg per day for 14 d, loss of intestinal epithelium is observed, consistent with the concept that Wnt is required for intestinal tissue homeostasis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	HN30 cells and UMSCC cells are used. For TaqMan assay, 2×10^6 cells per well are plated into six-well cell culture plates and treated with or without LGK974 in amultipoint dose-response. RNA samples are collected after 48 h. For colony formation assays, 2×10^3 cells per well are plated into six-well cell culture plates with or without compoundtreatment. Cells are stained with crystal violet 1 wk later[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice and Rats[1] Nude mice (or nude rats) bearing the mouse mammary tumor virus-Wnt1, HN30, or SNU1076 tumors are randomized according to tumor volume. LGK974 is formulated in 10% (vol/vol) citrate buffer (pH 2.8)/90% (vol/vol) citrate buffer (pH 3.0) or 0.5% MC/0.5% Tween 80 and administered by oral gavage at a dosing volume of 10 µL/g animal body weight. Body weight is monitored daily, and tumor sizes are assessed three times per week after the tumors are palpable. Tumor sizes are determined by using caliper measurements. Tumor volumes are calculated with a formula (length×width×height)/2. The plasma concentrations and exposures of LGK974 in the tumor-bearing nude mice (n=2 per dosing group) are determined on day 14. Blood samples (50 µL) are collected by serial retroorbital sampling at 1, 3, 7, 16, and 24 h postdose. The blood samples are centrifuged, and plasma is separated and frozen until analysis by liquid chromatography/MS/MS. For tolerability studies, LGK974 is administrated to nontumor-bearing Wistar rats one time per day by oral gavage at 3 or 20 mg/kg per day. Necropsies are performed at the end of the study. Tissues are fixed in 10% (vol/vol) neutralbuffered formalin, sectioned, and subjected to H&E staining. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2017 May 18;545(7654):355-359.
- Cell Stem Cell. 2020 Sep 3;27(3):413-429.e4.
- Sci Immunol. 2021 Nov 12;6(65):eabc6424.
- Nat Commun. 2019 Mar 27;10(1):1382.
- Oncogene. 2019 Mar;38(11):1951-1965.

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REFERENCES

[1]. Liu J, et al. 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.

[2]. Tammela T, et al. A Wnt-producing niche drives proliferative potential and progression in lung adenocarcinoma. Nature. 2017 May 18;545(7654):355-359.

Caution: Product has not been fully validated for medical applications. For research use only.

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