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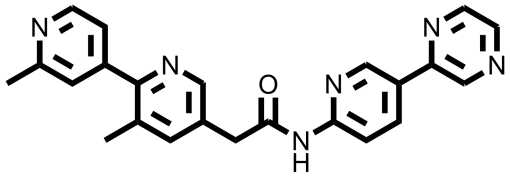
Porcupine (Wnt) Inhibitor – LGK974

Chemical Name: 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide



Molecular Weight:	396.44
Formula:	$C_{23}H_{20}N_6O$
Purity:	≥98%
CAS#:	1243244-14-5
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

LGK974 is a highly potent, selective and orally bioavailable Porcupine inhibitor (Wnt signaling antagonist) with an IC_{50} ~0.4 nM. LGK974 potently inhibits Wnt signaling in vitro and in vivo, including reduction of the Wnt-dependent LRP6 phosphorylation and the expression of Wnt target genes, such as AXIN2. LGK974 is potent and efficacious in multiple tumor models at well-tolerated doses in vivo, including murine and rat mechanistic breast cancer models driven by MMTV–Wnt1 and a human head and neck squamouscell carcinoma model (HN30). We also show that head and neck cancer cell lines with loss-of-function mutations in the Notch signaling pathway have a high response rate to LGK974. All LGK974-sensitive pancreatic cancer cell lines carried inactivating mutations of RNF43. Currently LGK974 is in the Phase I study to treat cancers that are driven by the Wnt pathway in a Wnt ligand-dependent manner.

How to Use:

In vitro: LGK974 was suggested to be used at 0.1 μM final concentration in vitro to completely block Wnt protein secretion.

In vivo: LGK974 was used to dose mice orally at 0.1-10 mg/kg once or twice per day to achieve good efficacy in xenograft models.

Reference:

1. Liu J, et al. Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974. (2013) Proc Natl Acad Sci USA. 110(50):20224-9.
2. Jiang X, et al. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. (2013) Proc Natl Acad Sci USA. 110(31):12649-54.
3. Shifeng Pan. Discovery of LGK974: A selective Porcupine inhibitor targeting Wnt signaling in cancer. AACR Annual Meeting 2013.