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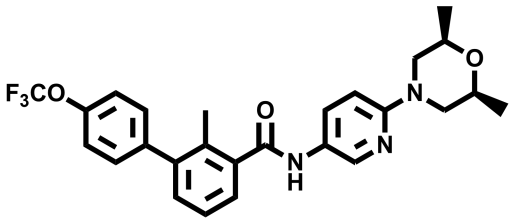
Hedgehog Antagonist LDE225

Chemical Name: N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4'-(trifluoromethoxy)biphenyl-3-carboxamide



Molecular Weight:	485.50
Formula:	$C_{26}H_{26}F_3N_3O_3$
Purity:	≥98%
CAS#:	956697-53-3
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

LDE225 is a potent and specific Hedgehog pathway inhibitor through binding and antagonizing Smo with an IC50 of 11 nM. It is currently in the clinical trials to treat cancers. It inhibited Hh signaling and induces tumor regression in animal models of medulloblastoma. It sensitized chemotherapy-resistant ovarian cancer cell lines to paclitaxel, but not to carboplatin. In one of the clinical trials, treatment with 0.75% LDE225 cream in NBCCS patients was very well tolerated and caused BCC regression.

How to Use:

In vitro: LDE225 was used at 1 μM final concentration in cellular assays.

In vivo: LDE225 was dosed orally at 20 mg/kg once per day or 10 mg/kg twice per day (formulation: PEG300/5% dextrose in water 75:25 v/v)

Reference:

1. Pan S, et al. Discovery of NVP-LDE225, a Potent and Selective Smoothened Antagonist. (2010) ACS Med. Chem. Lett., 1 (3), pp 130–134.
2. Buonamici S, et al. Interfering with resistance to smoothened antagonists by inhibition of the PI3K pathway in medulloblastoma. (2010) Sci Transl Med. 2(51):51ra70.
3. Skvara H, et al. Topical treatment of Basal cell carcinomas in nevoid Basal cell carcinoma syndrome with a smoothened inhibitor. (2011) J Invest Dermatol. 131(8):1735-44.
4. Steg AD, et al. Smoothened Antagonists Reverse Taxane Resistance in Ovarian Cancer. Mol Cancer Ther. 2012 in press.
5. Heller E, et al. Hedgehog signaling inhibition blocks growth of resistant tumors through effects on tumor microenvironment. (2012) Cancer Res. 72(4):897-907.