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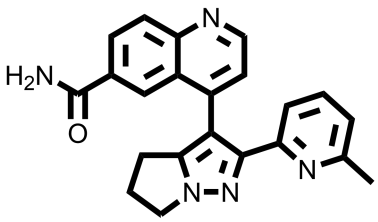
TGFβ Inhibitor LY2157299

Chemical Name: 4-(2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)quinoline-6-carboxamide



Molecular Weight:	369.42
Formula:	$C_{22}H_{19}N_5O$
Purity:	≥98%
CAS#:	700874-72-2
Solubility:	DMSO up to 100mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

LY2157299 is a novel potent and selective TGFβ receptor type I and type II (TβRI/II) inhibitor with IC_{50} of 86 nM and 2 nM, respectively. LY2157299 could inhibit the TGFβ induced Smad2 phosphorylation in HUVEC cells, promote VEGF induced HUVEC cell migration, and show dose dependent potentiation of VEGF or bFGF induced cell proliferation. It can also inhibit TGFβ–mediated Smad2 activation and hematopoietic suppression in primary hematopoietic stem cells in a dose-dependent manner. LY2157199 treatment stimulates hematopoiesis from primary MDS bone marrow specimens. In vivo administration of LY-2157299 ameliorated anemia in a TGF-β overexpressing transgenic mouse model of bone marrow failure. Oral administration of LY2157299 at 75 mg/kg/day displays significant antitumor activity against both Calu6 and MX1 xenografts in mice. LY2157299 in combination with lomustine (CCNU) more effectively blocks Smad phosphorylation than either agent alone, and significantly enhances the efficacy of lomustine in U87MG and CRL-2611 human glioblastoma xenografts. Currently LY2157299 is in phase I/II clinical trials for the treatment of glioma, HCC, and pancreatic cancer.

How to Use:

In vitro: LY2157299 was usually used at 5-10μM in vitro and cellular assays.

In vivo: LY2157299 was orally dosed to mice at 75mg/kg once per day or in combination with lomustine (CCNU) to significantly reduce the tumor volume.

Reference:

1. Zhou L, et al. Reduced SMAD7 leads to overactivation of TGF-beta signaling in MDS that can be reversed by a specific inhibitor of TGF-beta receptor I kinase. (2011) Cancer Res. 71(3):955-63.
2. Bueno L, et al. Semi-mechanistic modelling of the tumour growth inhibitory effects of LY2157299, a new type I receptor TGF-beta kinase antagonist, in mice. (2008) Eur J Cancer. 44(1):142-50.
3. Jonathan M, et al. A small molecule inhibitor of TGFß RI kinase potentiates VEGF dependent angiogenesis in vitro. (2006) Proc Amer Assoc Cancer Res, Volume 47, Abstract #250.
4. Liu Z, et al. VEGF and inhibitors of TGFbeta type-I receptor kinase synergistically promote blood-vessel formation by inducing alpha5-integrin expression. (2009) J Cell Sci. 122(Pt 18):3294-302.

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