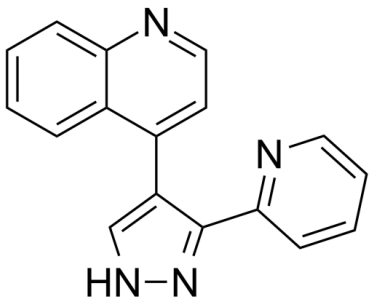
Data Sheet

Product Name:	LY-364947
Cat. No.:	CS-3451
CAS No.:	396129-53-6
Molecular Formula:	C17H12N4
Molecular Weight:	272.30
Target:	TGF-β Receptor
Pathway:	TGF-beta/Smad
Solubility:	DMSO : 25 mg/mL (91.81 mM; Need ultrasonic and warming); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

LY-364947 is a potent ATP-competitive inhibitor of **TGFβR-I** with **IC_{50}** of 59 nM, and exhibits 7-fold selectivity over TGFβR-II. IC50 & Target: IC50: 59 nM (TGFβR-I) **In Vitro:** LY-364947 is an ATP competitive and tight-binding inhibitor, inhibiting phosphorylation of P-Smad3 by TGFβR-I Kinase with K_i of 28 nM. LY-364947 inhibits in vivo Smad2 phosphorylation within the NMuMg cells with IC_{50} of 135 nM. LY-364947 reverses TGF-β-mediated growth inhibition in NMuMg cells with IC_{50} of 0.218 μM. LY-364947 potentiates the xVent2-lux BMP4 response in NMuMg cells by 30% at concentrations as low as 0.25 μM. LY-364947 (2 μM) prevents TGF-β-induced epithelial–mesenchymal transition in NMuMg cells[1]. LY-364947 (3 μM) induces expression of Prox1 and LYVE-1 in almost all HDLECs after 24 hours[2]. LY-364947 promotes nuclear export of Foxo3a, with low Smad2/3 and high Akt phosphorylation levels in leukaemia-initiating cells. LY-364947 (< 20 μM) suppresses leukaemia-initiating cells colony-forming ability after co-culture with OP-9 stromal cells[3]. **In Vivo:** LY-364947 (1 mg/kg, i.p.) accelerates lymphangiogenesis, as evidence by significantly increasing the LYVE-1-positive areas in a mouse model of chronic peritonitis. LY-364947 (1 mg/kg, i.p.) significantly increases the LYVE-1-positive areas in tumor tissues in tumor xenograft models using BxPC3 pancreatic adenocarcinoma cells[2]. LY-364947 (25 mg/kg) increases p-Akt and decreases nuclear Foxo3a in leukaemia-initiating cells in CML-affected mice[3].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]The IC_{50} of LY-364947 at different enzyme concentrations are determined by the filter-binding assay. Typically, 40 μL reactions in 50 mM HEPES at pH 7.5, 1 mM NaF, 200 μM pKSmad3(-3), and 50 mM ATP containing a titration of each inhibitor with concentrations of 1600, 800, 400, 200, 100, 50, 25, and 0 nM are incubated at 30°C for 30 min. The IC_{50} is calculated using a nonlinear regression method with GraphPad Prism software. The binding type is determined by plotting the correlation between enzyme concentrations and IC_{50} values. **Animal Administration:** LY-364947 is dissolved in 5 mg/mL in DMSO.[2]BALB/c nude mice 5 to 6 weeks of age are used in the assay. Parental, or VEGF-C- or TGF-β1-expressing tumor cells (5×10^6) in 100 μL PBS are implanted subcutaneously into male nude mice and allowed to grow for 2 to 3 weeks to reach proliferative phase, before initiation of TβR-I inhibitor administration. TβR-I inhibitor LY-364947, dissolved in 5 mg/mL in DMSO and diluted with 100 μL PBS, or the vehicle control, is injected intraperitoneally at 1 mg/kg, 3 times a week for 3 weeks. Excised samples are directly frozen in dry-iced acetone for immunohistochemistry. Frozen samples are further sectioned at 10-μm thickness in a cryostat and subsequently incubated with primary and secondary antibodies. Samples are observed using a confocal microscope.

References:

[1]. Peng SB, et al. Kinetic characterization of novel pyrazole TGF-beta receptor I kinase inhibitors and their blockade of the epithelial-mesenchymal transition. Biochemistry, 2005, 44(7), 2293-2304.

[2]. Oka M, et al. Inhibition of endogenous TGF-beta signaling enhances lymphangiogenesis. Blood, 2008, 111(9), 4571-4579.

[3]. Naka K, et al. TGF-beta-FOXO signalling maintains leukaemia-initiating cells in chronic myeloid leukaemia. Nature, 2010, 463(7281), 676-680.

CAIndexNames:

Quinoline, 4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-

SMILES:

C1(C2=CNN=C2C3=NC=CC=C3)=CC=NC4=CC=CC=C14

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