

Product Data Sheet

Product Name: LY2109761

Cat. No.: GC12363

Chemical Properties

Cas. No. 700874-71-1

Chemical Name 4-[2-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)quinolin-7-yl]oxyethyl]morpholine

SMILES C1CC2=C(C(=NN2C1)C3=CC=CC=N3)C4=C5C=CC(=CC5=NC=C4)OCCN6CCOCC6

Formula $C_{26}H_{27}N_5O_2$

M.Wt 441.52

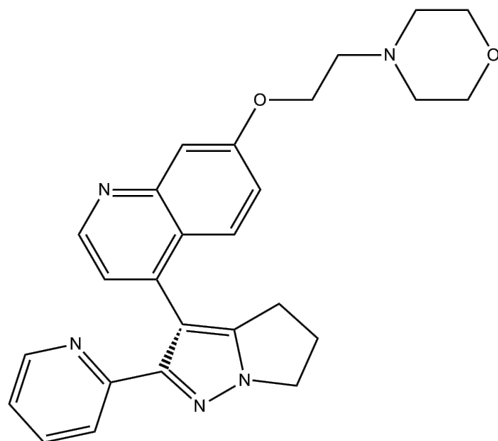
Solubility ≥ 22.1 mg/mL in DMSO

Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

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

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Cell experiment [1]:

Cell lines SKOV3 cells

SKOV3 cells were seeded at a density of 3.5×10^3 per well in 96-well microtiter culture plates. After overnight incubation, medium was removed and replaced with fresh medium containing different concentrations of LY2109761 (0.5-10 μ M) for 72h. On completion of incubation, viability was assessed after adding 50 μ L trypan blue solution (0.4% in PBS) in culture medium. After 1 to 2min, the number of dead cells, which retained the dye, was compared with the total number to calculate the percentage of viable cells.

Reaction Conditions 0.5-10 μ M; 72h

Applications LY2109761 treatment inhibited cell growth in a dose- and time-dependent manner.

Animal experiment [2]:

Animal models C57BL/6 mice

Female C57BL/6 mice were irradiated with a single dose of 20Gy photon radiation (RT) limited to the chest. LY2109761 was administered by oral gavage twice daily for 4 weeks at a dose of 50mg/kg body weight dissolved in 1% carboxymethylcellulose sodium (CMS) USP. Mice were randomly distributed to 6 groups group 1 (LY2109761, RT), LY2109761 treatment started 4 weeks before RT; group 2 (LY2109761, RT), LY2109761 treatment started 2 weeks before RT and continued for 2 weeks after RT; group 3 (RT, LY2109761), LY210976 started 1 day after RT; group 4 (LY2109761), LY2109761 was given over 4 weeks without RT; group 5 (RT), only RT; group 6 (control), only CMS.

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Dosage form 50mg/kg; po; twice daily for 4 weeks

Applications LY2109761 attenuates radiation-induced pulmonary fibrosis in mice by reversing TGF- β and BMP-related pro-inflammatory and pro-angiogenic signaling.

References:

- [1]. Gao Y, Shan N, Zhao C, et al. LY2109761 enhances cisplatin antitumor activity in ovarian cancer cells[J]. International journal of clinical and experimental pathology, 2015, 8(5): 4923.
- [2]. Flechsig P, Dadrich M, Bickelhaupt S, et al. LY2109761 attenuates radiation-induced pulmonary murine fibrosis via reversal of TGF- β and BMP-associated proinflammatory and proangiogenic signals[J]. Clinical Cancer Research, 2012, 18(13): 3616-3627.

Background

LY2109761 is an orally available, small-molecule dual TGF- β receptor (T β R) I/II kinase inhibitor (T β RI: K_i = 38nM; T β RII: K_i = 300nM) [1]. By blocking TGF- β signaling and inhibiting Smad2 phosphorylation, LY2109761 downregulates the TGF- β /Smad signaling pathway, exerting anti-proliferative and anti-invasive effects and inducing apoptosis [2-3]. LY2109761 is commonly used to treat cancer [4].

In SKOV3 cells, LY2109761 (0.5-10 μ M; 72h) treatment inhibited cell growth in a dose- and time-dependent manner [5]. In HepG2 cells, LY2109761 (0.1-100 μ M; 36h) inhibits cell proliferation by downregulating the phosphorylation of Smad-2 [6]. In AGS cells, LY2109761 (0-40 μ M; 2h) pretreatment inhibited cell proliferation in a dose-dependent manner after irradiation [7].

In C57BL/6 mice, LY2109761 (50mg/kg; po; twice daily for 4 weeks) attenuates radiation-induced pulmonary fibrosis in mice by reversing TGF- β and BMP-related pro-inflammatory and pro-angiogenic signaling [8]. In L3.6pl/GLT cells xenograft tumor mouse model, LY2109761 (50mg/kg; po; twice daily for 4 weeks) inhibits tumor growth and spontaneous metastasis in orthotopic xenografts in vivo [9].

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References:

- [1]. Sheen Y Y, Kim M J, Park S A, et al. Targeting the transforming growth factor- β signaling in cancer therapy[J]. Biomolecules & therapeutics, 2013, 21(5): 323.
- [2]. Wei G, Xu Q, Liu L, et al. LY2109761 reduces TGF- β 1-induced collagen production and contraction in hypertrophic scar fibroblasts[J]. Archives of Dermatological Research, 2018, 310(8): 615-623.
- [3]. Chen X, Yan H, Chen Y, et al. Moderate oxidative stress promotes epithelial–mesenchymal transition in the lens epithelial cells via the TGF- β /Smad and Wnt/ β -catenin pathways[J]. Molecular and cellular biochemistry, 2021, 476(3): 1631-1642.
- [4]. Connolly E C, Saunier E F, Quigley D, et al. Outgrowth of drug-resistant carcinomas expressing markers of tumor aggression after long-term T β RI/II kinase inhibition with LY2109761[J]. Cancer research, 2011, 71(6): 2339-2349.
- [5]. Gao Y, Shan N, Zhao C, et al. LY2109761 enhances cisplatin antitumor activity in ovarian cancer cells[J]. International journal of clinical and experimental pathology, 2015, 8(5): 4923.
- [6]. He X, Guo X, Zhang H, et al. Mechanism of action and efficacy of LY2109761, a TGF- β receptor inhibitor, targeting tumor microenvironment in liver cancer after TACE[J]. Oncotarget, 2017, 9(1): 1130.
- [7]. Yang T, Huang T, Zhang D, et al. TGF- β receptor inhibitor LY2109761 enhances the radiosensitivity of gastric cancer by inactivating the TGF- β /SMAD4 signaling pathway[J]. Aging (Albany NY), 2019, 11(20): 8892.
- [8]. Flechsig P, Dadrich M, Bickelhaupt S, et al. LY2109761 attenuates radiation-induced pulmonary murine fibrosis via reversal of TGF- β and BMP-associated proinflammatory and proangiogenic signals[J]. Clinical Cancer Research, 2012, 18(13): 3616-3627.
- [9]. Melisi D, Ishiyama S, Sclabas G M, et al. LY2109761, a novel transforming growth factor β receptor type I and type II dual inhibitor, as a therapeutic approach to suppressing pancreatic cancer metastasis[J]. Molecular cancer therapeutics, 2008, 7(4): 829-840.

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