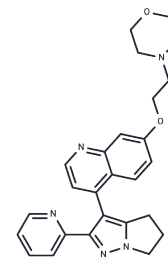


LY2109761

## Chemical Properties

CAS No. :	700874-71-1
Formula:	C <sub>26</sub> H <sub>27</sub> N <sub>5</sub> O <sub>2</sub>
Molecular Weight:	441.52
Storage:	Store at low temperature Powder: -20°C for 3 years   In solvent: -80°C for 1 year <small>Actual storage temperature shall be subject to the COA.</small>



## Biological Description

Description	LY2109761 is a novel selective TGF- $\beta$ receptor type I/II (T $\beta$ RI/II) dual inhibitor with $K_i$ of 38 nM and 300 nM, respectively; shown to negatively affect the phosphorylation of Smad2.
Targets(IC50)	Autophagy, TGF-beta/Smad
In vitro	Targeting T $\beta$ RI/II kinase activity with LY2109761 (5 $\mu$ M) almost completely suppressed both the basal ( $P = 0.0107$ ) and TGF- $\beta$ 1-stimulated migration of L3.6pl/GLT cells ( $P < 0.0001$ ), indicating that the migration of L3.6pl/GLT cells in vitro is effectively driven by endogenous TGF- $\beta$ [1]. LY2109761 (0.001-0.1 $\mu$ M) up-regulates ( $P < 0.001$ ) E-cadherin mRNA and protein levels. This increase was localized at the cellular membrane where E-cadherin mediates anchorage that is cell-cell dependent [2]. LY2109761 (10 $\mu$ M) or radiation (4 Gy) alone reduced neurosphere-forming efficiency in NMA-23 cells. The combination of LY2109761 plus radiation had supra-additive effects in neurosphere formation and limiting dilution assays [3].
In vivo	LY2109761 (50 mg/kg, p.o.) greatly reduced the tumor volume and increased the median survival duration of the mice to 45.0 days, but the differences were not significant. Only when LY2109761 was combined with gemcitabine were significant effects noted on tumor volume ( $P < 0.05$ ) and median survival duration, which was increased to 77.5 days ( $P = 0.0018$ ) [1]. In an orthotopic intracranial model, LY2109761 significantly reduced tumor growth, prolonged survival, and extended the prolongation of survival induced by radiation treatment. Histologic analyses showed that LY2109761 inhibited tumor invasion promoted by radiation, reduced tumor microvessel density, and attenuated mesenchymal transition [3].
Cell Research	LY2109761 cytotoxicity was determined by 3 methods: the MTT assay, manual counting of viable cells, and propidium iodide staining. MTT yields a purple formazan product that is detected using a 96-well plate reader at 570 nm. Cells were plated and cultured for 2 days in a 1% fetal bovine serum medium supplemented with LY2109761 at the following concentrations: 0.001, 0.01, 0.1, 1, 10, and 20 $\mu$ M. Each experimental condition was reproduced in 8 wells, and each experiment was repeated 3 times. To confirm the cytotoxic data, cells were incubated under the described conditions and stained with the vital dye trypan blue, which does not react with the cell membrane because of its negative charge. All the unstained cells were counted using a hemocytometer. Four squares were counted for each condition, and each condition was

Cell Research	repeated in triplicate in the same experiment. Each experiment was repeated 3 times for each cell line. Bars represent the average and standard deviation of all experiments. Under the same experimental conditions, nonpermeabilized cells were stained with propidium iodide and analyzed with a flow cytometer [2].
Animal Research	Three days after the orthotopic implantation of $1.0 \times 10^6$ L3.6pl/GLT tumor cells in 50 $\mu$ L of HBSS, when bioluminescence imaging confirmed that tumors were well established, 40 mice were randomly allocated into four groups (n = 10 mice per group) to receive one of the following treatments. (a) Vehicle solution for 50 $\mu$ L of LY2109761 twice a day p.o. (days 1-5 of each week) and 50 $\mu$ L of sterile saline daily i.p. (days 2 and 5 of each week; control group). (b) LY2109761 (50 mg/kg) twice a day p.o. (days 1-5 of each week) and 50 $\mu$ L of sterile saline daily i.p. (days 2 and 5 of each week). (c) Gemcitabine (25 mg/kg) daily i.p. (days 2 and 5 of each week) and p.o. vehicle for 50 $\mu$ L of LY2109761 twice a day (days 1-5 of each week). (d) LY2109761 (50 mg/kg) twice a day (days 1-5 of each week) and gemcitabine (25 mg/kg) daily i.p. (days 2 and 5 of each week). Treatments were continued for 4 wk. All mice were weighed weekly and observed for tumor growth. Tumor diameter was assessed with a Vernier caliper, and tumor volume (mm <sup>3</sup> ) was calculated as $d^2 \times D/2$ , wherein d and D represent the shortest and longest diameters, respectively. Bulky disease was considered present when the tumor burden was prominent in the mouse abdomen (tumor volume, $\geq 2,000$ mm <sup>3</sup> ). When at least 6 of 10 mice in a treatment group presented with bulky disease, the median survival duration for that group was considered to be reached. At the median survival duration of the control group, the tumor growth in mice in all groups was evaluated using the bioluminescence emitted by the tumor cells. Bioluminescence imaging was conducted using a cryogenically cooled IVIS 100 imaging system coupled to a data acquisition computer running Living Image software. The mice were sacrificed by carbon dioxide inhalation when evidence of advanced bulky disease was present. The day of sacrifice was considered the day of death for survival evaluation [1].

### Solubility Information

Solubility	DMSO: 6.875 mg/mL (15.57 mM),Sonication is recommended. Ethanol: Insoluble, H2O: Insoluble, ( $< 1$ mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 1 mg/mL (2.26 mM),Sonication is recommended. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

## Preparing Stock Solutions

	<b>1mg</b>	<b>5mg</b>	<b>10mg</b>
1 mM	2.2649 mL	11.3245 mL	22.649 mL
5 mM	0.453 mL	2.2649 mL	4.5298 mL
10 mM	0.2265 mL	1.1325 mL	2.2649 mL
50 mM	0.0453 mL	0.2265 mL	0.453 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

## Reference

- Melisi D, et al. LY2109761, a novel transforming growth factor beta receptor type I and type II dual inhibitor, as a therapeutic approach to suppressing pancreatic cancer metastasis. *Mol Cancer Ther.* 2008 Apr;7(4):829-40.
- Huang X, Han L, Wang R, et al. Dual-responsive nanosystem based on TGF- $\beta$  blockade and immunogenic chemotherapy for effective chemoimmunotherapy. *Drug Delivery.* 2022, 29(1): 1358-1369
- Lu Z Z, Sun C, Zhang X, et al. Neuropilin 1 is an entry receptor for KSHV infection of mesenchymal stem cell through TGFBR1/2-mediated macropinocytosis. *Science Advances.* 2023, 9(21): eadg1778.
- Fransvea E, et al. Blocking transforming growth factor-beta up-regulates E-cadherin and reduces migration and invasion of hepatocellular carcinoma cells. *Hepatology.* 2008 May;47(5):1557-66.
- Zhang M, et al. Blockade of TGF- $\beta$  signaling by the TGFBR-I kinase inhibitor LY2109761 enhances radiation response and prolongs survival in glioblastoma. *Cancer Res.* 2011 Dec 1;71(23):7155-67.
- Han L, Huang X, Zhao B, et al. TGF- $\beta$ 1 mediates tumor immunosuppression aggravating at the late stage post-high-light-dose photodynamic therapy. *Cancer Immunology, Immunotherapy.* 2023: 1-17.
- Ouyang S, Shi S, Ding W, et al. Neuropeptide Precursor VGF Promotes Liver Metastatic Colonization of G $\alpha$ q Mutant Uveal Melanoma by Facilitating Tumor Microenvironment via Paracrine Loops. *Advanced Science.* 2407967

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