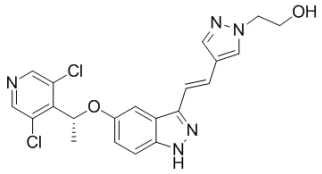
LY2874455

Cat. No.:	HY-13304
CAS No.:	1254473-64-7
Molecular Formula:	$C_{21}H_{19}Cl_2N_5O_2$
Molecular Weight:	444.31
Target:	FGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (112.53 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2507 mL	11.2534 mL	22.5068 mL
5 mM	0.4501 mL	2.2507 mL	4.5014 mL
10 mM	0.2251 mL	1.1253 mL	2.2507 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.63 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.63 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.63 mM); Suspended solution

BIOLOGICAL ACTIVITY

Description

LY2874455 is a pan-FGFR inhibitor with IC_{50}s of 2.8, 2.6, 6.4, 6 nM for FGFR1, FGFR2, FGFR3, FGFR4, respectively.

IC_{50} & Target

FGFR1	FGFR2	FGFR3	FGFR4
2.8 nM (IC_{50})	2.6 nM (IC_{50})	6.4 nM (IC_{50})	6 nM (IC_{50})

In Vitro

LY2874455 potently inhibits the Erk phosphorylation induced by FGF2 and FGF9 in both cell lines in a dose-dependent

	manner, with average IC_{50} values of 0.3 to 0.8 nM. LY2874455 indeed inhibits FGFR2 phosphorylation in SNU-16 and KATO-III cells, with estimated IC_{50} values of 0.8 and 1.5 nM, respectively. In addition, LY2874455 inhibits the phosphorylation of FRS2, an immediate downstream target of FGFR in these cell lines, again with a similar potency of 0.8 to 1.5 nM. Together, these results suggest that LY2874455 inhibits FGFR in the cell. The relative IC_{50} values of LY2874455 for KMS-11, OPM-2, L-363, and U266 cells are determined to be 0.57, 1.0, 60.4, and 290.7 nM, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	LY2874455 exhibits a rapid, robust, dose-dependent inhibition of tumor growth in all 4 models tested. Importantly, this molecule causes a significant regression of tumor growth in the RT-112, SNU-16, and OPM-2 tumor models, especially when dosed at 3 mg/kg twice a day. Also, LY2874455 exhibits an excellent pharmacokinetic/pharmacodynamic relationship as shown by its dose-dependent inhibition of the tumor growth at TED_{50} and TED_{90} (1 and 3 mg/kg, respectively). When tested in the RT-112 tumor xenograft model on an intermittent dosing schedule (twice a day 1 week on and 1 week off or twice a day 2 days on and 2 days off), LY2874455 is also efficacious. When rats are dosed with LY2874455 at 1 and 3 mg/kg, which is 2.6- and 7.7-fold over the TED_{50} (0.39 mg/kg) obtained in the rat heart IVTI assay, respectively, there are no significant changes observed in blood pressure. However, when rats are dosed with LY2874455 at 10 mg/kg, which is 25.6-fold over the TED_{50}, there are significant increases observed in arterial pressures[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Reaction mixtures contained 8 mM Tris-HCl (pH 7.5), 10 mM HEPES, 5 mM dithiothreitol, 10 μM ATP, 0.5 μCi ^{33}P-ATP, 10 mM $MnCl_2$, 150 mM NaCl, 0.01% Triton X-100, 4% DMSO, 0.05 mg/mL poly(Glu:Tyr) (4:1, average molecular weight of 20-50 kDa), and 7.5, 7.5, and 16 ng of FGFR1, FGFR3, and FGFR4, respectively, and are incubated at room temperature for 30 minutes followed by termination with 10% H_3PO_4. The reaction mixtures are transferred to 96-well MAFB filter plates that are washed 3 times with 0.5% H_3PO_4. After air-drying, the plates are read with a Trilux reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	The different multiple myeloma cancer cell lines KMS-11 and OPM-2 cells, L-363, and U266 cells are used. Cells (2,000 per well) are first grown in RPMI for 6 hours and treated with LY2874455 at 37°C for 3 days. The cells are stained at 37°C for 4 hours and then solubilized at 37°C for 1 hour. Finally, the plate is read at 570 nm using a plate reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] RT-112, OPM-2 (DSMZ), SNU-16, and NCI-H460 cells (RT-112: 2×10^6 per animal; OPM-2: 10^7 per animal; SNU-16: 10^6 per animal; and NCI-H460: 3×10^6 per animal) are mixed with Matrigel (1:1) and implanted subcutaneously into the rear flank of the mice (female, CD-1 nu/nu for RT-112, OPM-2, and NCI-H460 cells and female, severe combined immunodeficient for SNU-16 cells). The implanted tumor cells grow as solid tumors. To test the efficacy of LY2874455 in these models, the animals are orally dosed with approximately 1 mg/kg (TED_{50}) or 3 mg/kg (TED_{90}) of LY2874455 in 10% Acacia once (every day) or twice a day after tumors reach approximately 150 mm^3. The tumor volume and body weight are measured twice a week. Rats[1] Four male rats per group are dosed with vehicle (1% hydroxyethylcellulose, 0.25% polysorbate 80, and 0.05% Dow Corning antifoam 1510-US in purified water) on day 1 and LY2874455 (1, 3, and 10 mg/kg) on day 0. On day 1, at least 120 minutes of control data are collected following vehicle administration. On day 0, data are collected for approximately 20 hours beginning after the last animal is dosed. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450). pii: eaaq1093.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Zhao G, et al. A Novel, Selective Inhibitor of Fibroblast Growth Factor Receptors That Shows a Potent Broad Spectrum of Antitumor Activity in Several Tumor Xenograft Models. Molecular Cancer Therapeutics (2011), 10(11), 2200-2210.

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