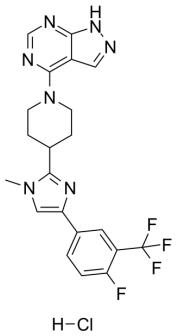
LY-2584702 hydrochloride

Cat. No.:	HY-12493B
CAS No.:	1082948-81-9
Molecular Formula:	$C_{21}H_{20}ClF_4N_7$
Molecular Weight:	481.88
Target:	Ribosomal S6 Kinase (RSK)
Pathway:	MAPK/ERK Pathway
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	LY-2584702 hydrochloride is a selective ATP competitive inhibitor of p70S6K with an IC_{50} of 4 nM. In S6K1 enzyme assay, the IC_{50} of LY-2584702 is 2 nM.

IC_{50} & Target	S6K1	p70S6K
	2 nM (IC_{50})	4 nM (IC_{50})

In Vitro	LY-2584702 (LY2584702) inhibits phosphorylation of the S6 ribosomal protein (pS6) in HCT116 colon cancer cells with an IC_{50} of 0.1-0.24 μM[1]. In S6K1 enzyme assay, the IC_{50} of LY-2584702 (LY2584702) is 2 nM. For pS6 inhibition in cells, the IC_{50}=100 nM. LY-2584702 has some activity against the S6K-related kinases MSK2 and RSK at high concentrations (enzyme assay IC_{50} =58-176 nM). LY-2584702 inhibits S6K activity in EOMA cells, as determined by the phosphorylation of its downstream effector S6, in a dose-dependent manner[2]. Proliferation of A549 is significantly inhibited by LY-2584702 (LY2584702) treating over 24 h at 0.1 μM ($P<0.05$); and the trend of decline is more conspicuous with longer treatment and/or with the increased drug concentration (all $P<0.05$). Similar results are also observed in SK-MES-1, although the obvious inhibition is led by LY-2584702 at 0.6 μM ($P<0.05$), much higher than that of A549[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	LY-2584702 demonstrates significant single-agent efficacy in both U87MG glioblastoma and HCT116 colon carcinoma xenograft models at two dose levels of 2.5 mg/kg twice daily (BID) and 12.5 mg/kg BID. LY-2584702 demonstrates statistically significant tumour growth reduction at TMED50 (threshold minimum effective dose 50%) (2.3 mg/kg) and TMED90 (10 mg/kg) in the HCT116 colon carcinoma xenograft model[1]. To examine the role of S6K in vivo, EOMA cells expressing shAkt3 are implanted in nu/nu mice, then treated for 14 days with LY-2584702 or Rapamycin. Analysis of tumors removed after 14 days shows that LY-2584702 inhibits S6 phosphorylation almost as effectively as Rapamycin. Loss of Akt3 increases tumor growth as compared with pLKO. LY-2584702 treatment alone does not significantly affect the growth of pLKO tumors. However, LY-2584702 significantly reduces the growth of tumors with shAkt3[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [3]	LY-2584702 is fully dissolved in 20 mL 10% DMSO and reserved at -80°C. When conducted the experiments in vitro, LY-2584702 is further diluted in 0.5% Tween 80, 5% propylene glycol and 30% PEG400 to reach different DMSO concentrations of 0.1 μM, 0.2 μM, 0.6 μM, and 1.0 μM. Cell Counting Kit-8 (CCK-8) is used to measure the cells proliferation in vitro. Cell lines

	A549 and SK-MES-1 treated by LY-2584702 for 24 h with different concentrations are seeded in 96-well plates at a density of 5×10^3 per well, with six repeats. DMSO treated, or in other words, the concentration of LY-2584702 of 0 is used as negative control. Cells absorbance at 450 nm is detected every 24 h after seeding to measure the proliferative activities[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] LY-2584702 is prepared in 0.25% Tween-80 and 0.05% antifoam, and administered orally to mice (12.5 mg/kg twice daily). EOMA cells (0.3×10^6) are injected subcutaneously in 6- to 8-week-old nu/nu female mice (2 sites/mouse, 4-5 mice/group). Tumor size is measured daily. For drug treatment, when tumors reach 0.01 cm^3 in size, the animals are treated with vehicle control or LY-2584702 (12.5 mg/kg twice daily, oral dosing). Tumor size is measured every 3 to 4 days[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Immunity. 2021 Sep 14;54(9):2042-2056.e8.
- Theranostics. 2022 Jan 1;12(3):1204-1219.
- Theranostics. 2022; 12(3):1204-1219.
- Pharmacol Res. 2021 Oct 4;105871.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Tolcher A, et al. A phase I trial of LY2584702 tosylate, a p70 S6 kinase inhibitor, in patients with advanced solid tumors. Eur J Cancer. 2014 Mar;50(5):867-75.

[2]. Phung TL, et al. Akt1 and akt3 exert opposing roles in the regulation of vascular tumor growth. Cancer Res. 2015 Jan 1;75(1):40-50.

[3]. Chen B, et al. Hyperphosphorylation of RPS6KB1, rather than overexpression, predicts worse prognosis in non-small cell lung cancer patients. PLoS One. 2017 Aug 9;12(8):e0182891.

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