Ralimetinib dimesylate

Cat. No.: HY-13241

CAS No.: 862507-23-1

Molecular Formula: $C_{26}H_{37}FN_6O_6S_2$

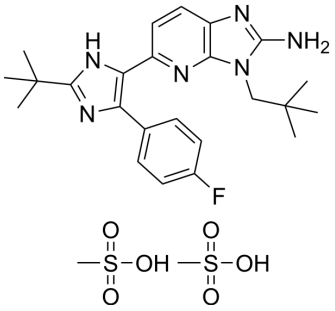
Molecular Weight: 612.74

Target: p38 MAPK; Autophagy; Apoptosis

Pathway: MAPK/ERK Pathway; Autophagy; Apoptosis

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 1 years; -20°C, 6 months (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 61 mg/mL (99.55 mM; Need ultrasonic and warming)

H_2O : ≥ 33.33 mg/mL (54.40 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6320 mL	8.1601 mL	16.3201 mL
	5 mM	0.3264 mL	1.6320 mL	3.2640 mL
	10 mM	0.1632 mL	0.8160 mL	1.6320 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 (4.08 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.08 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.08 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ralimetinib dimesylate (LY2228820 dimesylate) is a selective, ATP-competitive inhibitor of p38 MAPK α/β with IC_{50}s of 5.3 and 3.2 nM, respectively. Ralimetinib (LY2228820) selectively inhibits phosphorylation of MK2 (Thr334), with no effect on phosphorylation of p38a MAPK, JNK, ERK1/2, c-Jun, ATF2, or c-Myc.

IC_{50} & Target		
	p38β MAPK	p38α MAPK
	3.2 nM (IC_{50})	5.3 nM (IC_{50})

In Vitro	Ralimetinib dimesylate inhibits p38α, as well as the level of phosphoMAPKAPK-2 (pMK2) in RAW 264.7 cells, with IC_{50} values of 7 nM and 34.3 nM, respectively. Furthermore, Ralimetinib dimesylate inhibits lipopolysaccharide (LPS)-induced TNFα formation in murine peritoneal macrophages, with IC_{50} of 5.2 nM[1]. In multiple myeloma (MM) cells, including INA6, RPMI-8226, U266, and RPMI-Dox40, Ralimetinib dimesylate (LY2228820) (200 nM-800 nM) significantly blocks p38MAPK signaling, as revealed by its inhibition on phosphorylation of HSP27, a downstream target of p38MAPK, without affecting the expression level of HSP27. Ralimetinib dimesylate (200 nM-400 nM) enhances bortezomib-induced cytotoxicity and apoptosis, but Ralimetinib dimesylate alone doesn't inhibit the growth of MM.1S cells. Ralimetinib dimesylate (200 nM-800 nM) also inhibits secretion of IL-6 and MIP-1α in long-term BM stromal cells (LT-BMSCs), BM mononuclear cells (BMMNCs), peripheral blood (PB) $CD138^+$, $CD138^-$ or PB $CD14^+$ cells. Ralimetinib dimesylate (400 nM-800 nM) also blocks osteoclastogenesis from $CD14^+$ cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In LPS-induced mice, Ralimetinib dimesylate effectively inhibits the formation of TNFα with a threshold minimum 50% effective dose ($TMED_{50}$) less than 1 mg/kg. In a rat model of collagen-inducedarthritis (CIA), Ralimetinib dimesylate displays potent effects on paw swelling, bone erosion, and cartilage destruction, with a threshold minimum 50% effective dose ($TMED_{50}$)of 1.5 mg/kg[1]. Ralimetinib dimesylate inhibits tumor phospho-MK2 in a dose-dependent manner (TED_{50}=1.95 mg/kg, TED_{70}=11.17 mg/kg) in mice implanted with B16-F10 melanoma. Ralimetinib dimesylate inhibits MK2 phosphorylation: mouse in vivo TED_{50}=1.01 mg/kg (compound exposure approximately 100 nM) and human ex vivo IC_{50} =0.12 μM with either mouse or human PBMC[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Inhibition of p38α is determined using recombinant human p38α in a standard filter binding protocol using ATP[γ-^{33}P] and EGFR 21-mer peptide as substrate. Functional inhibition of TNFα in murine peritoneal macrophages is determined using LPS stimulation in the presence of Ralimetinib. To assess p38α activity in cells more directly, RAW 264.7 cells are treated with Ralimetinib and then stimulated with anisomycin. The level of p38α activity is detected using a phosphoMAPKAPK-2 (pMK2) (Thr 334) antibody which reacts with a residue specifically phosphorylated by p38α. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Murine B16-F10 melanoma cells are cultured in Dulbecco's Modified Eagle Medium supplemented with l-glutamine, high glucose and 10% FBS (GIBCO 11965-092). C57/bl6 mice are implanted in the rear flank with B16-F10 cells (2×10^6), and when tumors reach approximately 200 mm^3 in size, are dosed orally with Ralimetinib dimesylate in 1% carboxymethylcellulose/0.25% Tween 80. Two hours postdose, tumors are excised, homogenized, and lysed for Western blot analysis. MK2 phosphorylation (p-Thr334), normalized to total glyceraldehyde-3-phosphate dehydrogenase, is quantified by chemiluminescent detection. The 50% or 70% threshold effective dose (TED_{50} and TED_{70}, respectively) is calculated to approximate effective dose ranges for testing of Ralimetinib dimesylate in xenograft models, that is, where significant target inhibition is observed. The TED_{50} or TED_{70} is defined as the dose where a statistically significant effect is achieved, and there is at least 50% or 70% inhibition, respectively, compared with vehicle control. 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):eaaq1093.
- Nat Commun. 2021 Dec 3;12(1):6941.
- EBioMedicine. 2015 Nov 19;2(12):1944-56.
- Cell Death Dis. 2021 Oct 23;12(11):994.
- Cell Rep. 2023 Mar 20;42(3):112275.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. Mader M, et al. Imidazolyl benzimidazoles and imidazo[4,5-b]pyridines as potent p38alpha MAP kinase inhibitors with excellent in vivo antiinflammatory properties. Bioorg Med Chem Lett, 2008, 18(1), 179-183.

[2]. Ishitsuka K, et al. p38 mitogen-activated protein kinase inhibitor LY2228820 enhances bortezomib-induced cytotoxicity and inhibits osteoclastogenesis in multiple myeloma; therapeutic implications. Br J Haematol, 2008, 141(5), 598-606.

[3]. Campbell RM, et al. Characterization of LY2228820 dimesylate, a potent and selective inhibitor of p38 MAPK with antitumor activity. Mol Cancer Ther. 2014 Feb;13(2):364-74.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA