# 产品名称：LY2228820
# 产品别名：Ralimetinib dimesylate；LY2228820 dimesylate

## 生物活性：

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| **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 ($IC_{50}$) |

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| **In Vitro** | Ralimetinib dimesylate inhibits p38α, as well as the level of phosphoMAPKAPK-2 (pMK2) in RAW 264.7 cells, with IC50 values of 7 nM and 34.3 nM, respectively. Furthermore, Ralimetinib dimesylate inhibits lipopolysaccharide (LPS)-induced TNFα formation in murine peritoneal macrophages, with IC50 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]. |
| **In Vivo** | In LPS-induced mice, Ralimetinib dimesylate effectively inhibits the formation of TNFα with a threshold minimum 50% effective dose (TMED50) 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 (TMED50)of 1.5 mg/kg[1]. Ralimetinib dimesylate inhibits tumor phospho-MK2 in a dose-dependent manner (TED50=1.95 mg/kg, TED70=11.17 mg/kg) in mice implanted with B16-F10 melanoma. Ralimetinib dimesylate inhibits MK2 phosphorylation: mouse in vivo TED50=1.01 mg/kg (compound exposure approximately 100 nM) and human ex vivo IC50=0.12 μM with either mouse or human PBMC[3]. |

**Solvent&Solubility**

***In Vitro:***

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

| Preparing Stock Solutions | Solvent / Mass / 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 |

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

***In Vivo:***

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出

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| | 现沉淀、析出现象，可以通过加热和/或超声的方式助溶<br>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline<br>Solubility: ≥ 2.5 mg/mL (4.08 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (4.08 mM，饱和度未知) 的澄清溶液。<br>以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。<br>2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)<br>Solubility: ≥ 2.5 mg/mL (4.08 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (4.08 mM，饱和度未知) 的澄清溶液。<br>以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。<br>3.请依序添加每种溶剂： 10% DMSO →90% corn oil<br>Solubility: ≥ 2.5 mg/mL (4.08 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (4.08 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。<br>以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀 |
| **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.<br>[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.<br>[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. |

**实验参考：**

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| **Animal Administration** | 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 ($2\times10^6$), 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. [3] |
| **Kinase Assay** | Inhibition of p38α is determined using recombinant human p38α in a standard filter binding protocol using ATP[$\gamma$-$^{33}$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. [1] |

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| **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.<br>[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.<br>[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. |