Ralimetinib dimesylate

Cat. No.: HY-13241
CAS No.: 862507-23-1
Molecular Formula: C₂₆H₃₇FN₆O₆S₂
Molecular Weight: 612.74
Target: p38 MAPK
Pathway: MAPK/ERK Pathway
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: 61 mg/mL (99.55 mM; Need ultrasonic and warming)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparing</td>
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<tr>
<td>Stock Solutions</td>
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<tr>
<td>Concentration</td>
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<tr>
<td>1 mM</td>
<td>1.632 mL</td>
<td>8.1601 mL</td>
<td>16.3201 mL</td>
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<tr>
<td>5 mM</td>
<td>0.3264 mL</td>
<td>1.6320 mL</td>
<td>3.2640 mL</td>
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<tr>
<td>10 mM</td>
<td>0.1632 mL</td>
<td>0.8160 mL</td>
<td>1.6320 mL</td>
</tr>
</tbody>
</table>

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

BIOLOGICAL ACTIVITY

Description
Ralimetinib dimesylate (LY2228820 dimesylate) is a selective, ATP-competitive inhibitor of p38 MAPK α/β with IC₅₀ values of 5.3 and 3.2 nM, respectively.

IC₅₀ & Target
IC₅₀: 5.3 nM (p38 MAPK α), 3.2 nM (p38 MAPK β) [3]

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 [2]. 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-induced arthritis (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[3]. 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].

PROTOCOL

Kinase Assay [1]

Inhibition of p38α is determined using recombinant human p38α in a standard filter binding protocol using ATP[γ-33P] 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/b6 mice are implanted in the rear flank with B16-F10 cells (2×10⁶), and when tumors reach approximately 200 mm³ 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 (TED50 and TED70, 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 TED50 or TED70 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.

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REFERENCES

