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产品名称: **MCC950**  
产品别名: **CP-456773; CRID3**

生物活性:					
Description	MCC950 (CP-456773; CRID3) is a potent and selective NLRP3 inhibitor with IC50s of 7.5 and 8.1 nM in BMDMs and HMDMs, respectively.				
IC <sub>50</sub> & Target	IC50: 7.5 nM (NLRP3, in BMDMs), 8.1 nM (NLRP3, in HMDMs)[1]				
In Vitro	MCC950 blocks canonical and non-canonical NLRP3 activation at nanomolar concentrations. MCC950 specifically inhibits NLRP3 but not AIM2, NLRC4 or NLRP1 activation. The effect of MCC950 on NLRP3 inflammasome activation is tested in mouse bone marrow derived macrophages (BMDM) and human monocyte derived macrophages (HMDM). The IC50 of MCC950 in BMDM is approximately 7.5 nM, while in HMDM it has a similar inhibitory capacity (IC50=8.1 nM). MCC950 also dose dependently inhibit IL-1β but not TNF-α secretion.MCC950 specifically blocks caspase-11-directed NLRP3 activation and IL-1β secretion upon stimulation of the non-canonical pathway. NLRC4-stimulated IL-1β and TNF-α secretion (as activated by Salmonella typhimurium) are not inhibited by MCC950 even at a concentration of 10 μM. MCC950 does not inhibit caspase-1 activation or IL-1β processing in response to S. typhimurium. The expression of pro-caspase-1 and pro-IL-1β in cell lysates is not substantially affected by MCC950 treatment[1].				
In Vivo	MCC950 reduces Interleukin-1p (IL-1β) production and attenuates the severity of experimental autoimmune encephalomyelitis (EAE), a disease model of multiple sclerosis. Pre-treatment with MCC950 reduces serum concentrations of IL-1β and IL-6 while it does not considerably decrease the amount of TNF-α. Treatment of mice with MCC950 delays the onset and reduced the severity of EAE. Intracellular cytokine staining and FACS analysis of brain mononuclear cells from mice sacrificed on day 22 shows modestly reduced frequencies of IL-17 and IFN-γ producing CD3+ T cells in MCC950 treated mice in comparison with PBS-treated mice. IFN-γ and particularly IL-17 producing cell numbers are also reduced in both the CD4+ and γδ+ sub-populations of CD3+ T cells[1].				
<div><b>In Vitro:</b></div> <div>H<sub>2</sub>O : 50 mg/mL (123.62 mM; Need ultrasonic)</div> <div>DMSO : ≥ 28 mg/mL (69.22 mM)</div> <div>* "≥" means soluble, but saturation unknown.</div>					
<table><tr><th rowspan="4">Preparing  </th></tr></table>					Preparing  
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<b>Solvent&amp;Solubility</b>	<p>备液, 再依次添加助溶剂:</p> <p>——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; 如在配制过程中出现沉淀、析出现象, 可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂: 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: <math>\geq 2.5</math> mg/mL (6.18 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (6.18 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 400 <math>\mu</math>L PEG300 中, 混合均匀向上述体系中加入 50 <math>\mu</math>L Tween-80, 混合均匀; 然后继续加入 450 <math>\mu</math>L 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂: 10% DMSO→ 90% (20% SBE-<math>\beta</math>-CD in saline)</p> <p>Solubility: <math>\geq 2.5</math> mg/mL (6.18 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (6.18 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 20% 的 SBE-<math>\beta</math>-CD 生理盐水水溶液中, 混合均匀。</p> <p>3.请依序添加每种溶剂: 10% DMSO →90% corn oil</p> <p>Solubility: <math>\geq 2.5</math> mg/mL (6.18 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (6.18 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。</p> <p>以 1 mL 工作液为例, 取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 玉米油中, 混合均匀。</p>
<b>References</b>	<p>[1]. Coll RC, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. Nat Med. 2015 Mar;21(3):248-55.</p> <p>[2]. Gan W, et al. The SGK1 inhibitor EMD638683, prevents Angiotensin II-induced cardiac inflammation and fibrosis by blocking NLRP3 inflammasome activation. Biochim Biophys Acta. 2017 Oct 3;1864(1):1-10.</p> <p>[3]. Zhang XY, et al. Propofol Does Not Reduce Pyroptosis of Enterocytes and Intestinal Epithelial Injury After Lipopolysaccharide Challenge. Dig Dis Sci. 2018 Jan;63(1):81-91.</p> <p>[4]. Qi Y, et al. NLRP3-dependent synaptic plasticity deficit in an Alzheimer's disease amyloidosis model in vivo. Neurobiol Dis. 2018 Feb 23;114:24-30.</p>
<b>实验参考:</b>	
<b>Cell Assay</b>	<p>BMDM are seeded at <math>5 \times 10^5</math>/mL or <math>1 \times 10^6</math>/mL, HMDM at <math>5 \times 10^5</math>/mL and PBMC at <math>2 \times 10^6</math>/mL or <math>5 \times 10^6</math>/mL in 96 well plates. The following day the overnight medium is replaced and cells are stimulated with 10 ng/mL LPS from <i>Escherichia coli</i> serotype EH100 (ra) TLRgrad for 3 h. Medium is removed and replaced with serum free medium (SFM) containing DMSO (1:1,000), MCC950 (0.001-10 <math>\mu</math>M), glyburide (200 <math>\mu</math>M), Parthenolide (10 <math>\mu</math>M) or Bayer cysteinyl leukotriene receptor antagonist</p> <p>1-(5-carboxy-2{3-[4-(3-cyclohexylpropoxy)phenyl]propoxy}benzoyl)piperidine-4-carboxylic acid (40 <math>\mu</math>M) for 30 min. Cells are then stimulated with inflammasome activators: 5 mM adenosine 5'-triphosphate disodium salt hydrate (ATP) (1 h), 1 <math>\mu</math>g/mL Poly(deoxyadenylic-thymidylic) acid sodium salt (Poly dA:dT) transfected with Lipofectamine 200 (3-4 h), 200 <math>\mu</math>g/mL MSU (overnight)</p>



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	<p>and 10 <math>\mu</math>M nigericin (1 h) or <i>S. typhimurium</i> UK-1 strain. Cells are also stimulated with 25 <math>\mu</math>g/mL Polyadenylic-polyuridylic acid (4 h). For non-canonical inflammasome activation cells are primed with 100 ng/mL Pam3CSK4 for 4 h, medium is removed and replaced with SFM containing DMSO or MCC950 and 2 <math>\mu</math>g/mL LPS is transfected using 0.25% FuGENE for 16 h. Supernatants are removed and analysed using ELISA kits. LDH release is measured using the CytoTox96 non-radioactive cytotoxicity assay[1].</p>
<b>Animal Administration</b>	<p>Mice[1]</p> <p>C57BL/6 mice are immunized subcutaneously with 150 <math>\mu</math>g of MOG peptide 35-55 emulsified in CFA containing 4 mg/mL (0.4.mg/mouse) of heat-killed MTB. Mice are injected i.p. with 500 ng pertussis toxin (PT: kaketsuken) on days 0 and 2. MCC950 is administered i.p. to mice (10 mg/kg) at induction of the disease, day 0, 1 and 2 and every 2 days thereafter. Control mice are administered vehicle (PBS) at the same time points. Mice are observed for clinical signs of disease daily (unblinded). Disease severity is scored as follows: no clinical signs, 0; limp tail, 1; ataxic gait, 2; hind limb weakness, 3; hind limb paralysis, 4; and tetra paralysis, 5.</p>
<b>References</b>	<p>[1]. Coll RC, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. <i>Nat Med</i>. 2015 Mar;21(3):248-55.</p> <p>[2]. Gan W, et al. The SGK1 inhibitor EMD638683, prevents Angiotensin II-induced cardiac inflammation and fibrosis by blocking NLRP3 inflammasome activation. <i>Biochim Biophys Acta</i>. 2017 Oct 3;1864(1):1-10.</p> <p>[3]. Zhang XY, et al. Propofol Does Not Reduce Pyroptosis of Enterocytes and Intestinal Epithelial Injury After Lipopolysaccharide Challenge. <i>Dig Dis Sci</i>. 2018 Jan;63(1):81-91.</p> <p>[4]. Qi Y, et al. NLRP3-dependent synaptic plasticity deficit in an Alzheimer's disease amyloidosis model in vivo. <i>Neurobiol Dis</i>. 2018 Feb 23;114:24-30.</p>

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