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产品名称: **CC-401 (hydrochloride)**  
产品别名: **CC401 HCl**

<b>生物活性:</b>				
<b>Description</b>	CC-401 hydrochloride is a potent inhibitor of all three forms of JNK with $K_i$ of 25 to 50 nM.			
<b>IC<sub>50</sub> &amp; Target</b>	JNK			
	25-50 nM ( $K_i$ )			
<b>In Vitro</b>	CC-401 has at least 40-fold selectivity for JNK compared with other related kinases, including p38, extracellular signal-regulated kinase (ERK), inhibitor of $\kappa$ B kinase (IKK2), protein kinase C, Lck, zeta-associated protein of 70 kDa (ZAP70). In cell-based assays, 1 to 5 $\mu$ M CC-401 provides specific JNK inhibition. CC-401, a small molecule that is a specific inhibitor of all three JNK isoforms. CC-401 competitively binds the ATP binding site in JNK, resulting in inhibition of the phosphorylation of the N-terminal activation domain of the transcription factor c-Jun. The specificity of this inhibitor is tested in vitro using osmotic stress of the HK-2 human tubular epithelial cell line. CC-401 inhibits sorbitol-induced phosphorylation of c-Jun in a dosage-dependent manner. However, CC-401 does not prevent sorbitol-induced phosphorylation of JNK, p38, or ERK <sup>[1]</sup> .			
<b>In Vivo</b>	The staining of p-JNK is moderately induced in bevacizumab and Oxaliplatin treatments as compared to control, and in the CC-401-treated samples p-cJun content is significantly lower, consistent with effective JNK inhibition. DNA damage is modestly elevated in combined treatments with CC-401 <sup>[2]</sup> . CC-401 treatment from days 7 to 24 slows the progression of proteinuria, which is significantly reduced compared to the no-treatment and vehicle groups at days 14 and 21. However, there is still an increase in the degree of proteinuria at day 21 in CC-401-treated rats compared to proteinuria at day 5. The vehicle and no-treatment groups developed renal impairment at day 24 as shown by an increase in serum creatinine. This is prevented by CC-401 treatment <sup>[3]</sup> .			
<b>Solvent&amp;Solubility</b>	<b>In Vitro:</b> DMSO : 100 mg/mL (235.33 mM; Need ultrasonic)			
	<b>Preparing Stock Solutions</b>	<b>Solvent</b>	<b>Mass</b>	<b>Concentration</b>
		<b>1 mM</b>	<b>2.3533 mL</b>	<b>5 mg</b>
		<b>5 mM</b>	<b>0.4707 mL</b>	<b>10 mg</b>
		<b>10 mM</b>	<b>0.2353 mL</b>	<b>1.1767 mL</b>
	*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。 <b>In Vivo:</b> 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; 如在配制过程中出现沉淀、析出现象, 可以通过加热和/或超声的方式助溶			



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	<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 (5.88 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (5.88 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 (5.88 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (5.88 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 (5.88 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (5.88 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>
References	<p>[1]. Ma FY, et al. A pathogenic role for c-Jun amino-terminal kinase signaling in renal fibrosis and tubular cell apoptosis. J Am Soc Nephrol. 2007 Feb;18(2):472-84.</p> <p>[2]. Vasilevskaya IA, et al. Inhibition of JNK Sensitizes Hypoxic Colon Cancer Cells to DNA-Damaging Agents. Clin Cancer Res. 2015 Sep 15;21(18):4143-52.</p> <p>[3]. Ma FY, et al. Blockade of the c-Jun amino terminal kinase prevents crescent formation and halts established anti-GBM glomerulonephritis in the rat. Lab Invest. 2009 Apr;89(4):470-84.</p>
实验参考:	
Cell Assay	<p>Human HK-2 proximal tubular epithelial cells are cultured in DMEM/F12 media supplemented with 10% FCS, 10 ng/mL EGF, and 10 <math>\mu</math>g/mL bovine pituitary extract. For Western blot studies, cells are seeded into six-well plates and allowed to adhere overnight, and medium is changed to DMEM/F12 supplemented with only 0.5% FCS for 24 h, by which time cells are confluent. CC-401 is prepared in citric acid (pH 5.5) and added to the confluent cells 1 h before the addition of 300 mM sorbitol, and cells are harvested 30 min later using urea-RIPA buffer. Three experiments are performed, each with two replicates per condition. For ELISA experiments, HK-2 cells are seeded into 24-well plates, allowed to adhere overnight, cultured in DMEM/F12 with 0.5% FCS for 24 h, and then incubated with CC-401 or vehicle for 60 min before stimulation with 1 <math>\mu</math>M Angiotensin II (AngII). Supernatants are harvested 48 h later and assayed for TGF-<math>\beta</math>1 content using a commercial ELISA kit. Three experiments are performed, each using six replicates per condition<sup>[1]</sup>.</p>
	<p>Mice<sup>[2]</sup></p> <p>To assess the efficacy of JNK signaling inhibition by CC-401 in anti-angiogenic and Oxaliplatin combination therapy in a mouse xenograft model, adult (8-10 weeks of age) female severe combined immunodeficient mice (C.B.17 SCID) are used. To generate tumors, HT29 cells (<math>1 \times 10^6</math> cells) are injected subcutaneously into the left flank of the mice. When the tumors reached</p>



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<b>Animal Administration</b>	<p>approximately 200 mm<sup>3</sup>, mice are divided into eight groups (eight mice per group) for treatment with Bevacizumab, Oxaliplatin, CC401, and the appropriate combinations of Bevacizumab, Oxaliplatin and CC-401. Mice in the Bevacizumab treatment group receive 5 mg/kg of Bevacizumab by intraperitoneal injection every 3 days for 21 days. The Oxaliplatin treatment group is injected intraperitoneally with 5 mg/kg Oxaliplatin per week for 2 weeks. The CC-401 treatment group is injected intraperitoneally 25 mg/kg for every 3 days. The combination treatment groups receive Bevacizumab (every 3 days, 5 mg/kg), Oxaliplatin (weekly for 2 weeks, 5 mg/kg), and CC-401 (every 3 days, 25 mg/kg). The control group receive saline intraperitoneally. Tumor volume and body weight are measured every 3 days. Tumor volume is calculated. Tumor growth delay is calculated as the difference in the time for control and treated tumors to grow from 200 to 800 mm<sup>3</sup>. For tumor growth delay calculations, mice are continued to receive treatments till the tumor volume reached 800 mm<sup>3</sup>. For immunohistochemistry mice are sacrificed after treatments on day 9 for tumor processing and staining.</p> <p>Rats<sup>[3]</sup></p> <p>Female WKY rats (180-220 g) are used. Groups of 9 or 10 rats are immunized by subcutaneous injection of 5 mg of sheep IgG in Freund's complete adjuvant followed 5 days later (termed day 0) by a tail vein injection of sheep anti-rat GBM serum. In this study, CC-401 (200 mg/kg/b.i.d. by oral gavage) or vehicle (sodium citrate) treatment is initiated in groups of 9 or 10 rats at 7 days after anti-GBM serum administration and continued twice daily thereafter until animals are killed at day 24. Additional groups of rats without treatment are killed at day 7 or day 24 after anti-GBM serum injection as controls. Animals are housed in metabolic cages for 22 hours to collect urine on days 5, 14, and 21. Blood is collected at the time of death. Analysis of serum creatinine and urinary protein are performed.</p>
<b>References</b>	<p>[1]. Ma FY, et al. A pathogenic role for c-Jun amino-terminal kinase signaling in renal fibrosis and tubular cell apoptosis. J Am Soc Nephrol. 2007 Feb;18(2):472-84.</p> <p>[2]. Vasilevskaya IA, et al. Inhibition of JNK Sensitizes Hypoxic Colon Cancer Cells to DNA-Damaging Agents. Clin Cancer Res. 2015 Sep 15;21(18):4143-52.</p> <p>[3]. Ma FY, et al. Blockade of the c-Jun amino terminal kinase prevents crescent formation and halts established anti-GBM glomerulonephritis in the rat. Lab Invest. 2009 Apr;89(4):470-84.</p>