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产品名称: **Exatecan (Mesylate)**  
产品别名: 依沙替康甲磺酸盐 ; **DX8951f**

生物活性:				
Description	Exatecan Mesylate is a DNA topoisomerase I inhibitor, with an IC <sub>50</sub> of 2.2 μM (0.975 μg/mL), and can be used in cancer research.			
IC <sub>50</sub> & Target	Topoisomerase I			
	2.2 μM (IC <sub>50</sub> )			
In Vitro	Exatecan Mesylate is a potent topoisomerase I inhibitor, with an IC <sub>50</sub> of 0.975 μg/mL. Exatecan Mesylate (DX-8951f) significantly inhibits the proliferation of several cancer cell lines, with mean GI <sub>50</sub> s of 2.02 ng/mL, 2.92 ng/mL, 1.53 ng/mL, and 0.877 ng/mL for breast cancer cells, colon cancer cells, stomach cancer cells and lung cancer cells, respectively <sup>[1]</sup> . Exatecan Mesylate (DX-8951f) displays cytotoxic activities against PC-6, PC-6/SN2-5 cells, with mean GI <sub>50</sub> s of 0.186 and 0.395 ng/mL, respectively. Exatecan Mesylate (34 nM) stabilizes DNA-TopoI complexes in PC-6 and PC-6/SN2-5 cells <sup>[3]</sup> .			
In Vivo	Exatecan Mesylate (DX-8951f, 3.325-50 mg/kg, i.v.) exhibits antitumor activities in the mice model bearing tumor cells, without toxic death <sup>[1]</sup> . Exatecan Mesylate (15, 25 mg/kg, i.v.) highly inhibits MIA-PaCa, BxPC-3 primary tumor growth in the MIA-PaCa-2 early-stage model and early-stage model of BxPC-3. Exatecan Mesylate (15, 25 mg/kg, i.v.) also significantly suppresses BxPC-3 lymphatic metastasis and completely eliminates lung metastasis in the BxPC-3 late-stage cancer model <sup>[2]</sup> .			
Solvent&Solubility	<b>In Vitro:</b> DMSO : 8.33 mg/mL (15.67 mM; Need ultrasonic) H <sub>2</sub> O : 6 mg/mL (11.29 mM; Need ultrasonic and warming)			
	Preparing Stock Solutions	Solvent Concentration	Mass	
			1 mg	
			5 mg	
			10 mg	
		1 mM	1.8813 mL	9.4065 mL
		5 mM	0.3763 mL	1.8813 mL
		10 mM	0.1881 mL	0.9406 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℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用，-20℃ 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 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 0.83 mg/mL (1.56 mM); Clear solution 此方案可获得 ≥ 0.83 mg/mL (1.56 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 8.3 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；			



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	<p>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 <math>\rightarrow</math> 90% (20% SBE-<math>\beta</math>-CD in saline)</p> <p>Solubility: <math>\geq 0.83</math> mg/mL (1.56 mM); Clear solution</p> <p>此方案可获得 <math>\geq 0.83</math> mg/mL (1.56 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 8.3 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]. Mitsui I, et al. A new water-soluble camptothecin derivative, DX-8951f, exhibits potent antitumor activity against human tumors in vitro and in vivo. Jpn J Cancer Res. 1995 Aug;86(8):776-82.</p> <p>[2]. Sun FX, et al. Efficacy of camptothecin analog DX-8951f (Exatecan Mesylate) on human pancreatic cancer in an orthotopic metastatic model. Cancer Res. 2003 Jan 1;63(1):80-5.</p> <p>[3]. Joto N, et al. DX-8951f, a water-soluble camptothecin analog, exhibits potent antitumor activity against a human lung cancer cell line and its SN-38-resistant variant. Int J Cancer. 1997 Aug 7;72(4):680-6.</p>
实验参考:	
Cell Assay	<p>Growth inhibition experiments are carried out in 96-well flat-bottomed microplates, and the amount of viable cell at the end of the incubation is determined by MTT assay. Thus, 500-20000 cells/well in 150 <math>\mu</math>L of medium are plated and grown for 24 h (P388, CCRF-CEM and K562 cells for 4h), the drug (including Exatecan Mesylate, in 150 <math>\mu</math>L medium/well), or the medium alone as a control, is added, and the cells are cultured for an additional 3 days. After addition of MTT (20 <math>\mu</math>L/well, 5 mg/mL in phosphate-buffered saline), the plates are incubated for 4 h and centrifuged at 800 g for 5 min, then the medium is removed and the blue dye formed is dissolved in 150 <math>\mu</math>L of DMSO. the absorbance is measured at 540 nm using a Microplate Reader model 3550<sup>[1]</sup>.</p>
Animal Administration	<p>At 3 weeks after BxPC-3-GFP and MIA-PaCa-2-GFP orthotopic implantation, mice are randomized into five different groups of 5 mice each for treatment purposes. Group 1 serves as the negative control and does not receive any treatment. Groups 2 and 3 are treated with Exatecan Mesylate at 25 and 15 mg/kg/dose, respectively. Groups 4 and 5 receive gemcitabine treatments at 300 and 150 mg/kg/dose, respectively. At 6 weeks after BxPC-3-GFP orthotopic implantation, mice are randomized into three different groups of 20 mice each for treatment purposes. Group 1 serves as the negative control and does not receive any treatment. Group 2 is treated with 25 mg/kg/dose Exatecan Mesylate and group 3 receives 300 mg/kg/dose gemcitabine. Dosing for both drugs is performed once a week for 3 weeks, discontinued for 2 weeks, and then continued for another 3 weeks. In both early and late cancer models, primary tumor size and body weights are measured once a week. Tumor volumes are calculated using the formula <math>a \times b^2 \times 0.5</math>, where a and b represent the larger and smaller diameters, respectively. At the termination of the studies, mice are sacrificed and explored. Final tumor weights and direct GFP images of primary tumor and metastases are recorded for each mouse. The tumor growth IR is calculated using the formula <math>IR (\%) = (1 - TW_t/TW_c) \times 100</math>, where <math>TW_t</math> and <math>TW_c</math> are the mean tumor weight of treated and control groups, respectively<sup>[2]</sup>.</p>
	<p>Cells (<math>5 \times 10^6</math>) are lysed with SDS buffer (10 mM HEPES, 2 mM orthovanadate, 10 mM NaF, 10 mM pyrophosphate, 1 mM PMSF, 10 <math>\mu</math>g/mL leupeptin, 10% 2-mercaptoethanol, 10% glycerol, 8% SDS,</p>



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<b>Kinase Assay</b>	<p>42 mM Tris-HCl, 0.002% bromophenol blue, pH 7.4). Protein in the whole cell lysates is separated in 7.5% polyacryl-amide gel and blotted onto nitrocellulose membrane. The membrane is treated with anti-Topo I human antibody and subsequently, with horseradish peroxidase-conjugated protein A. The Topo I-specific band is detected with ECL reagents. To obtain a nuclear extract, cells (<math>5 \times 10^7</math>) are washed with ice-cold buffer (2 mM <math>K_2HPO_4</math>, 5 mM <math>MgCl_2</math>, 150 mM NaCl, 1 mM EGTA, 0.1 mM dithiothreitol), resuspended in buffer containing 0.35% Triton-X100 and PMSF and then incubated on ice for 10 min. The resulting lysates are centrifuged, and precipitates are then incubated with buffer containing 0.35 M NaCl for 1 hr at 4°C. After centrifugation (18,000g, 10 min), the protein concentration of the supernatant (nuclear extract) is determined using a protein assay kit. The same amount of nuclear protein is analyzed by Western blotting analysis using anti-Topo I antibody<sup>[3]</sup>.</p>
<b>References</b>	<p>[1]. Mitsui I, et al. A new water-soluble camptothecin derivative, DX-8951f, exhibits potent antitumor activity against human tumors in vitro and in vivo. <i>Jpn J Cancer Res.</i> 1995 Aug;86(8):776-82.</p> <p>[2]. Sun FX, et al. Efficacy of camptothecin analog DX-8951f (Exatecan Mesylate) on human pancreatic cancer in an orthotopic metastatic model. <i>Cancer Res.</i> 2003 Jan 1;63(1):80-5.</p> <p>[3]. Joto N, et al. DX-8951f, a water-soluble camptothecin analog, exhibits potent antitumor activity against a human lung cancer cell line and its SN-38-resistant variant. <i>Int J Cancer.</i> 1997 Aug 7;72(4):680-6.</p>

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