



上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话: 021-61312973 传真: 021-55068248
网址: www.shyuanye.com
邮箱: shyysw@sina.com

产品名称: 尼罗替尼
产品别名: **Nilotinib**; 尼洛替尼; **AMN107**

生物活性:

Description	Nilotinib is an orally available Bcr-Abl tyrosine kinase inhibitor with antineoplastic activity.				
IC ₅₀ & Target	Bcr-Abl[1]				
In Vitro	The novel, selective Abl inhibitor, Nilotinib (AMN107), is designed to interact with the ATP-binding site of BCR-ABL with a higher affinity than Imatinib. In addition to being significantly more potent compared with Imatinib (IC ₅₀ <30 nM), Nilotinib also maintains activity against most of the BCR-ABL point mutants that confer Imatinib resistance[1]. Nilotinib demonstrates significant antitumor efficacy against GIST xenograft lines and Imatinib-resistant GIST cell lines. The parent cell lines GK1C and GK3C show Imatinib sensitivity with IC ₅₀ of 4.59±0.97 μM and 11.15±1.48 μM, respectively. The Imatinib-resistant cell lines GK1C-IR and GK3C-IR show Imatinib resistance with IC ₅₀ values of 11.74±0.17 μM (P<0.001) and 41.37±1.07 μM (P<0.001), respectively[2].				
In Vivo	The percentage of tumor growth inhibition (TGI) is 83.8% for Imatinib and 69.6% for Nilotinib in the GK1X xenograft line (n.s.). In the GK2X xenograft line, TGI is 83.0% for Imatinib and 85.3% for Nilotinib (n.s.). Additionally, the GK3X xenograft line TGI is 31.1% for Imatinib and 47.5% for Nilotinib (n.s.). These results suggest that, except for the GK1X xenograft line, Nilotinib shows equivalent or higher antitumor effects than Imatinib[2]. Nilotinib has a significant healing effect on the macroscopic and microscopic pathologic scores and ensures considerable mucosal healing in the indomethacin-induced enterocolitis rat model. While Nilotinib decreased the PDGFR α and β levels and apoptotic scores in the colon, it did not have a significant effect on the weight and TNF-α levels. Further experimental investigations could provide more definitive evidence for humans[3].				
Solvent&Solubility	In Vitro: DMSO : 6 mg/mL (11.33 mM; Need ultrasonic) H₂O : < 0.1 mg/mL (insoluble)				
	Preparing Stock Solutions	Solvent Mass Concentration	1 mg	5 mg	10 mg
		1 mM	1.8885 mL	9.4425 mL	18.8850 mL
		5 mM	0.3777 mL	1.8885 mL	3.7770 mL
		10 mM	0.1889 mL	0.9443 mL	1.8885 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。 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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	1.请依序添加每种溶剂: 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 0.6 mg/mL (1.13 mM); Clear solution 此方案可获得 ≥ 0.6 mg/mL (1.13 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例, 取 100 μL 6.0 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。 2.请依序添加每种溶剂: 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 0.6 mg/mL (1.13 mM); Suspended solution 此方案可获得 ≥ 0.6 mg/mL (1.13 mM, 饱和度未知) 的均匀悬浊液, 悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例, 取 100 μL 6.0 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。 3.请依序添加每种溶剂: 10% DMSO →90% corn oil Solubility: ≥ 0.6 mg/mL (1.13 mM); Clear solution 此方案可获得 ≥ 0.6 mg/mL (1.13 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。 以 1 mL 工作液为例, 取 100 μL 6.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。
References	[1]. Weisberg E, et al. Beneficial effects of combining nilotinib and imatinib in preclinical models of BCR-ABL+ leukemias. Blood. 2007 Mar 1;109(5):2112-20. [2]. Sako H, et al. Antitumor effect of the tyrosine kinase inhibitor Nilotinib on gastrointestinal stromal tumor (GIST) and Imatinib-resistant GIST cells. PLoS One. 2014 Sep 15;9(9):e107613. [3]. Dervis Hakim G, et al. Mucosal healing effect of nilotinib in indomethacin-induced enterocolitis: A rat model. World J Gastroenterol. 2015 Nov 28;21(44):12576-85. [4]. Fujita KI, et al. Involvement of the Transporters P-Glycoprotein and Breast Cancer Resistance Protein in Dermal Distribution of the Multikinase Inhibitor Regorafenib and Its Active Metabolites. J Pharm Sci. 2017 Sep;106(9):2632-2641. [5]. Meirson T, et al. Targeting invadopodia-mediated breast cancer metastasis by using ABL kinase inhibitors. Oncotarget. 2018 Apr 24;9(31):22158-22183.
实验参考:	
Cell Assay	The human GIST cell lines GK1C and GK3C, and the Imatinib-resistant cell lines GK1C-IR and GK3C-IR are plated in 96-well microplates and cultured for 12 h before exposure to Imatinib (1-100 μM) or Nilotinib (1-100 μM) for 72 h. The cells are quantified by the WST-8 assay. The optical density (OD) is determined with Sunrise rainbow. The rate of inhibition is calculated as follows: % of inhibition=(OD of treated group-blank)/(OD of control group-blank)$\times$100%. The concentration of tested drugs resulting in 50% growth inhibition (IC50) is calculated[2].
	Mice^[2] The GIST xenograft lines GK1X, GK2X and GK3X in nude mice are used. These xenograft lines are maintained by continual passage in BALB/cSLC-<i>nu/nu</i> mice. Mice bearing GK1X, GK2X and GK3X tumors (6-8 mice per group) are treated daily with vehicle or 40 mg/kg Imatinib or Nilotinib for 4 weeks. Tumor volume (TV) is determined from caliper measurements of tumor length (L) and width



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Animal Administration	(w) according to the formula $LW^2/2$. TV is determined every two to three days and on the day of evaluation. Mice are sacrificed and the percentage of tumor growth inhibition (TGI) is calculated as follows: $TGI (\%) = [1 - (\text{mean of treatment group tumor volume on evaluation day} - \text{mean of treatment group tumor volume on day 1}) / (\text{mean of control group tumor volume on evaluation day} - \text{mean of control group tumor volume on day 1})] \times 100$. Rats^[3] Female Wistar albino rats, weighing 226-243 g (mean weight, 241.09 g), for use in this study. Nilotinib, administered 20 mg/kg/d in two divided doses, is administered to the Nilotinib group of rats (n=7) for 13 d through an orogastric tube, beginning on the same day as indomethacin administration. Blood and tissue samples for pathological examination are obtained from all rats under ether anesthesia at the end of the 13-d period. All animals are then sacrificed by decapitation.
References	[1]. Weisberg E, et al. Beneficial effects of combining nilotinib and imatinib in preclinical models of BCR-ABL+ leukemias. Blood. 2007 Mar 1;109(5):2112-20. [2]. Sako H, et al. Antitumor effect of the tyrosine kinase inhibitor Nilotinib on gastrointestinal stromal tumor (GIST) and Imatinib-resistant GIST cells. PLoS One. 2014 Sep 15;9(9):e107613. [3]. Dervis Hakim G, et al. Mucosal healing effect of nilotinib in indomethacin-induced enterocolitis: A rat model. World J Gastroenterol. 2015 Nov 28;21(44):12576-85. [4]. Fujita KI, et al. Involvement of the Transporters P-Glycoprotein and Breast Cancer Resistance Protein in Dermal Distribution of the Multikinase Inhibitor Regorafenib and Its Active Metabolites. J Pharm Sci. 2017 Sep;106(9):2632-2641. [5]. Meirson T, et al. Targeting invadopodia-mediated breast cancer metastasis by using ABL kinase inhibitors. Oncotarget. 2018 Apr 24;9(31):22158-22183.

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