



上海源叶生物科技有限公司
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产品名称: **MLN4924 (hydrochloride)**
产品别名: **Pevonedistat hydrochloride**

生物活性:					
Description	Pevonedistat hydrochloride (MLN4924 hydrochloride) is a potent and selective NEDD8-activating enzyme (NAE) inhibitor, with an IC50 of 4.7 nM.				
IC50 & Target	IC50: 4.7 nM (NAE)				
In Vitro	Pevonedistat (MLN4924) is a potent inhibitor of NAE (half-maximal inhibitory concentration (IC50=0.004 μM), and is selective relative to the closely related enzymes UAE, SAE, UBA6 and ATG7 (IC50=1.5, 8.2, 1.8 and >10 μM, respectively). Pevonedistat (MLN4924) treatment inhibits overall protein turnover in cultured HCT-116 cells. Treatment of HCT-116 cells with Pevonedistat (MLN4924) for 24 h results in a dose-dependent decrease of Ubc12-NEDD8 thioester and NEDD8-cullin conjugates, with an IC50 < 0.1 μM, resulting in a reciprocal increase in the abundance of the known CRL substrates CDT1, p27 and NRF2 (also known as NFE2L2), but not non-CRL substrates[1]. Pevonedistat induces CLL cell apoptosis and circumvented stroma-mediated resistance. Pevonedistat promotes induction of Bim and Noxa in the CLL cells leading to rebalancing of Bcl-2 family members toward the proapoptotic BH3-only proteins[2]. Pevonedistat (MLN4924) rapidly inhibits cullin 1 neddylation and remarkably suppressed growth and survival as well as migration in a dose- and time-dependent manner in gastric cancer cells, and significantly suppresses migration by transcriptionally activating E-cadherin and repressing MMP-9[3].				
In Vivo	Pevonedistat (MLN4924, 30 or 60 mg/kg, s.c.) leads to a dose- and time-dependent increase in the steady state levels of NRF2 and CDT1 in HCT-116 tumour-bearing mice, and decreases NEDD8-cullin levels in normal mouse tissue as illustrated in mouse bone marrow cells. Pevonedistat (MLN4924) administered on a BID schedule at 30 and 60 mg/kg inhibits tumour growth with T/C values of 0.36 and 0.15, respectively[1].				
Solvent&Solubility	In Vitro:				
	DMSO : 100 mg/mL (208.34 mM; Need ultrasonic)				
	Preparing Stock Solutions	Solvent Mass Concentration	1 mg	5 mg	10 mg
		1 mM	2.0834 mL	10.4171 mL	20.8342 mL
		5 mM	0.4167 mL	2.0834 mL	4.1668 mL
	10 mM	0.2083 mL	1.0417 mL	2.0834 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: ≥ 2.5 mg/mL (5.21 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.21 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例, 取 100 μL 25.0 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: ≥ 2.5 mg/mL (5.21 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.21 mM, 饱和度未知) 的澄清溶液。 以 1 mL 工作液为例, 取 100 μL 25.0 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: ≥ 2.5 mg/mL (5.21 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.21 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 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。
References	[1]. Soucy TA, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature. 2009 Apr 9;458(7239):732-6. [2]. J. Claire Godbersen, e tal. The Nedd8-Activating Enzyme Inhibitor MLN4924 Thwarts Microenvironment-Driven NF-κB Activation and Induces Apoptosis in Chronic Lymphocytic Leukemia B Cells. [3]. Lan H, et al. Neddylation inhibitor MLN4924 suppresses growth and migration of human gastric cancer cells. Sci Rep. 2016 Apr 11;6:24218.
实验参考:	
Cell Assay	HCT-116 cells grown in 6-well cell-culture dishes are treated with 0.1% DMSO (control) or Pevonedistat(MLN4924) for 24 h. Whole cell extracts are prepared and analysed by immunoblotting. For analysis of the E2-UBL thioester levels, lysates are fractionated by non-reducing SDS-PAGE and immunoblotted with polyclonal antibodies to Ubc12, Ubc9 and Ubc10. For analysis of other proteins, lysates are fractionated by reducing SDS-PAGE and probed with primary antibodies as follows: mouse monoclonal antibodies to CDT1, p27, geminin, ubiquitin, securin/PTTG and p53 or rabbit polyclonal antibodies to NRF2, Cyclin B1 and GADD34. Rabbit monoclonal antibodies to NEDD8 and phosphorylated CHK1 (Ser 317) are generated using Ac-KEIEIDIEPTDKVERIKERVEE-amide and Ac-VKYSS(pS)QPEPRT-amide as immunogens, respectively. Antibodies to pH3, cleaved PARP and cleaved caspase 3 are from Cell Signaling Technologies. Secondary HRP-labelled antibodies to rabbit IgG or mouse IgG are used as appropriate. Blots are developed with ECL reagent. [1]
Animal Administration	Female athymic NCR mice are used in all in vivo studies. Mice are inoculated with 2$\times$10⁶ HCT-116 cells (or 30-40 mg H522 tumour fragments) subcutaneously in the right flank, and tumour growth is monitored with caliper measurements. When the mean tumour volume reaches approximately 200



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	mm3, animals are dosed subcutaneously with vehicle (10% cyclodextrin) or Pevonedistat (MLN4924). Inhibition of tumour growth (T/C) is calculated on the last day of treatment. [1]
References	[1]. Soucy TA, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature. 2009 Apr 9;458(7239):732-6. [2]. J. Claire Godbersen, et al. The Nedd8-Activating Enzyme Inhibitor MLN4924 Thwarts Microenvironment-Driven NF-κB Activation and Induces Apoptosis in Chronic Lymphocytic Leukemia B Cells. [3]. Lan H, et al. Neddylation inhibitor MLN4924 suppresses growth and migration of human gastric cancer cells. Sci Rep. 2016 Apr 11;6:24218.



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