Pevonedistat hydrochloride

Cat. No.: HY-10484

CAS No.: 1160295-21-5

Molecular Formula: $C_{21}H_{26}ClN_5O_4S$

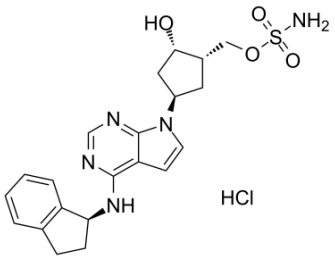
Molecular Weight: 479.98

Target: NEDD8-activating Enzyme

Pathway: Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (208.34 mM; Need ultrasonic)

H_2O : 10 mg/mL (20.83 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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.21 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pevonedistat hydrochloride (MLN4924 hydrochloride) is a potent and selective NEDD8-activating enzyme (NAE) inhibitor, with an IC_{50} of 4.7 nM[1].

IC_{50} & Target

IC50: 4.7 nM (NAE)[1]

In Vitro

Pevonedistat (MLN4924) is a potent inhibitor of NAE (half-maximal inhibitory concentration (IC_{50}=0.004 μM), and is selective

	relative to the closely related enzymes UAE, SAE, UBA6 and ATG7 (IC_{50}=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 IC_{50} < 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Pevonedistat (MLN492410, 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Female athymic NCR mice are used in all in vivo studies. Mice are inoculated with 2×10^6 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 mm^3, 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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2020 Dec;588(7836):164-168.
- Cell. 2019 Jul 11;178(2):330-345.e22.
- Cancer Cell. 2020 Mar 16;37(3):371-386.e12.
- Cell Res. 2021 Mar;31(3):291-311.
- Nat Microbiol. 2019 May;4(5):813-825.

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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.

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