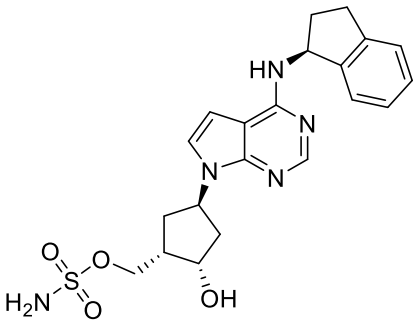
Product data sheet

MedKoo Cat#: 201924 Name: Pevonedistat (MLN-4924) CAS#: 905579-51-3 (free base) Chemical Formula: $C_{21}H_{25}N_5O_4S$ Exact Mass: 443.16273 Molecular Weight: 443.52	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Pevonedistat, also known as MLN-4924 and TAK-924, is a small molecule inhibitor of Nedd8 activating enzyme (NAE) with potential antineoplastic activity. NAE inhibitor MLN4924 binds to and inhibits NAE, which may result in the inhibition of tumor cell proliferation and survival. NAE activates Nedd8 (Neural precursor cell expressed, developmentally down-regulated 8), an ubiquitin-like (UBL) protein that modifies cellular targets in a pathway that is parallel to but distinct from the ubiquitin-proteasome pathway (UPP).

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	20.0	45.1

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.25 mL	11.27 mL	22.55 mL
5 mM	0.45 mL	2.25 mL	4.51 mL
10 mM	0.23 mL	1.13 mL	2.25 mL
50 mM	0.05 mL	0.23 mL	0.45 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Milhollen MA, Traore T, Adams-Duffy J, Thomas MP, Berger AJ, Dang L, Dick LR, Garnsey JJ, Koenig E, Langston SP, Manfredi M, Narayanan U, Rolfe M, Staudt LM, Soucy TA, Yu J, Zhang J, Bolen JB, Smith PG. MLN4924, a NEDD8-activating enzyme inhibitor, is active in diffuse large B-cell lymphoma models: rationale for treatment of NF-{kappa}B-dependent lymphoma. Blood. 2010 Sep 2;116(9):1515-23. doi: 10.1182/blood-2010-03-272567. Epub 2010 Jun 4. PMID: 20525923.

2. Soucy TA, Smith PG, Milhollen MA, Berger AJ, Gavin JM, Adhikari S, Brownell JE, Burke KE, Cardin DP, Critchley S, Cullis CA, Doucette A, Garnsey JJ, Gaulin JL, Gershman RE, Lublinsky AR, McDonald A, Mizutani H, Narayanan U, Olhava EJ, Peluso S, Rezaei M, Sintchak MD, Talreja T, Thomas MP, Traore T, Vyskocil S, Weatherhead GS, Yu J, Zhang J, Dick LR, Claiborne CF, Rolfe M, Bolen JB, Langston SP. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature. 2009 Apr 9;458(7239):732-6. doi: 10.1038/nature07884. PMID: 19360080.

In vivo study

1. Milhollen MA, Traore T, Adams-Duffy J, Thomas MP, Berger AJ, Dang L, Dick LR, Garnsey JJ, Koenig E, Langston SP, Manfredi M, Narayanan U, Rolfe M, Staudt LM, Soucy TA, Yu J, Zhang J, Bolen JB, Smith PG. MLN4924, a NEDD8-activating enzyme

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7. Bioactivity

Biological target:

MLN4924 is a small molecule inhibitor of Nedd8 activating enzyme (NAE) with IC50 of 4 nM.

In vitro activity

Treatment of HCT-116 cells with MLN4924 for 24 h resulted in a dose-dependent decrease of Ubc12-NEDD8 thioester and NEDD8-cullin conjugates, with an IC50,0.1 mM (Fig. 3a), resulting in a reciprocal increase in the abundance of the known CRL substrates CDT1 (refs 22-24), p27 (refs 14, 25) and NRF2 (also known as NFE2L2)26, but not non- CRL substrates (Supplementary Fig. 3). In similar experiments, the accumulation of other CRL substrates including c-Jun27, HIF1a (ref. 28), cyclin E29, CDC25A (ref. 30), EMI1 (also known as FBXO5)31 and phosphorylated IkBa (refs 13, 32) was observed (data not shown). The observed accumulation of CRL substrates in MLN4924- treated HCT-116 cells is consistent with the idea that the abundance of most, if not all, CRL target proteins can be modulated by NAE inhibition. HCT-116 cells were treated with 0.3 mM MLN4924, a concentration sufficient to decrease the steady-state level of NEDD8-cullin conjugates by.80% relative to untreated cells (Fig. 3a, dashed outline), and the cell-cycle profiles were monitored by DNA content using flow cytometry. As early as 8 h after compound treatment, cells began to accumulate in S-phase (Fig. 3b). By 24 h, a significant fraction of cells contained$4N DNA content (Fig. 3b, dashed outline); however, the absence of detectable phosphohistone H3 (pH3) staining indicated that the cells were not transitioning into mitosis (Fig. 3a). By 48 h, an increase in the sub-2N DNA content population was observed, consistent with cells undergoing apoptosis and further supported by the accumulation of cleaved caspase 3 and PARP (Fig. 3a).

Reference: Nature. 2009 Apr 9;458(7239):732-6. https://doi.org/10.1038/nature07884

In vivo activity

To assess the ability of MLN4924 to inhibit NAE in vivo, HCT-116 tumour-bearing mice received a single subcutaneous dose of 10, 30 or 60mgkg21 MLN4924, and tumours were excised at various timepoints over the subsequent 24 h period. The pharmacodynamic effects of treatment were assessed in tumour lysates which were analysed for NEDD8-cullin, NRF2 and CDT1 protein levels (Fig. 4a-c). A single dose of MLN4924 resulted in a dose- and time-dependent decrease of NEDD8-cullin levels as early as 30 min after administration of compound (Fig. 4a), with maximal effect 1-2 h post-dose. A significant difference was observed between the 10 and 60 mgkg21 response profiles (P,0.01), although the 10 and 30mgkg21 (P50.11) and 30 and 60 mg kg21 (P50.24) profiles were not significantly different from each other. A single dose of MLN4924 also led to a dose- and time-dependent increase in the steady state levels of NRF2 and CDT1 (Fig. 4b, c). For all dose levels, NRF2 protein levels peaked 2-4 h after administration ofMLN4924 and started to decline by 4-8 h post-dose. The timing of CDT1 accumulation was slightly delayed compared to NRF2, peaking 4 h after MLN4924 administration (Fig. 4c). Evidence of DNA damage in the tumour was indicated by the increased levels of phosphorylated CHK1 (Ser 317) at 8 h after a single administration of 30 and 60 mgkg21 MLN4924 (Fig. 4d). It should be noted that MLN4924 also decreased NEDD8-cullin levels in normal mouse tissue as illustrated in mouse bone marrow cells (Supplementary Fig. 5). These data suggest that MLN4924-mediated inhibition of NAE in this in vivo tumour model results in pathway responses and cellular phenotypic effects compatible with those observed in cultured cells.

Reference: Nature. 2009 Apr 9;458(7239):732-6. https://doi.org/10.1038/nature07884