

Product Data Sheet

Product Name: MLN4924

Cat. No.: GC15086

Chemical Properties

Cas. No. 905579-51-3

Chemical Name [(1S,2S,4R)-4-[4-[[[(1S)-2,3-dihydro-1H-inden-1-yl]amino]pyrrolo[2,3-d]pyrimidin-7-yl]-2-hydroxycyclopentyl]methyl sulfamate

SMILES C1CC2=CC=CC=C2C1NC3=NC=NC4=C3C=CN4C5CC(C(C5)O)COS(=O)(=O)N

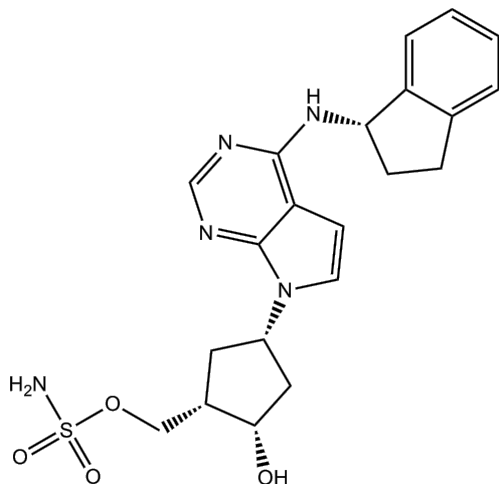
Formula $C_{21}H_{25}N_5O_4S$ M.Wt 443.53

Solubility $\geq 22.2\text{mg/mL}$ in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

Cell lines HCT-116 cells

Caution: Product has not been fully validated for medical applications. For research use only.

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HCT-116 cells grown in 6-well cell-culture dishes were treated with 0.1% DMSO (control) or MLN4924 for 24 h. Whole cell extracts were prepared and analysed by immunoblotting. For analysis of the E2-UBL thioester levels, lysates were fractionated by non-reducing SDS-PAGE and immunoblotted with polyclonal antibodies to Ubc12, Ubc9 and Ubc10.

Reaction Conditions
0-3µM for 24 hours

Applications
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 µM

Animal experiment [1]:

Animal models
Female athymic NCR mice

All animals were housed and handled in accordance with the Guide for the Care and Use of Laboratory Animals. Mice were inoculated with 2 × 10⁶ HCT-116 cells (or 30-40 mg H522 tumour fragments) subcutaneously in the right flank, and tumour growth was monitored with caliper measurements. When the mean tumour volume reached approximately 200 mm³, animals were dosed subcutaneously with vehicle (10% cyclodextrin) or MLN4924. Inhibition of tumour growth (T/C) was calculated on the last day of treatment.

Dosage form
subcutaneous injection, once (QD) or twice (BID) daily, 30 and 60 mg kg⁻¹

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Applications MLN4924 administered on a BID schedule at 30 and 60 mg kg⁻¹ inhibited tumour growth with T/C values of 0.36 and 0.15, respectively

References:

[1]: Soucy T A, Smith P G, Milhollen M A, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer[J]. Nature, 2009, 458(7239): 732-736.

Background

MLN4924 is a potent and selective small-molecule inhibitor of NEDD8-activating enzyme (NAE) (IC₅₀ = 4 nM) [1,2], 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) [2]. MLN4924 has a multifaceted mechanism of action that is characterized by the induction of DNA re-replication and DNA damage, increased oxidative stress, inhibition of NF-κB activity, apoptotic cell death, and cellular senescence [3].

MLN4924 Treatment of HCT-116 cells for 24 h resulted in a dose-dependent decrease of Ubc12-NEDD8 thioester and NEDD8-cullin conjugates, with an IC₅₀ < 0.1 µM [2], resulting in a reciprocal increase in the abundance of the known CRL substrates CDT1, p27 and NRF2 (also known as NFE2L2), c-Jun27, HIF1α, cyclin E29, CDC25A, EMI1 (also known as FBXO5) and phosphorylated IκBα, but not non-CRL substrates [2]. MLN4924 treatment of human-tumour-derived cell lines, including HCT-116(colon), Calu-6 (lung), SKOV-3 (ovarian), H460 (lung), DLD-1 (colon), CWR22 (prostate) and OCI-LY19 (lymphoma), resulted in S-phase-defective phenotypes [2]. Potent inhibition of MLN4924 of cell viability was observed across 17 lymphoma cell lines tested in an ATPlite viability assay, with EC₅₀ values of 10 to 244nM [1].

In OCI-Ly10 xenografts, a dose- and time-dependent increase in pIκBα levels was observed after MLN4924 treatment (10, 30, or 60 mg/kg, subcutaneous), with peak elevation occurring 2 hours after dose and levels returning to baseline at 8 hours after dose. A consequence of inhibiting NAE and NF-κB signaling in OCI-Ly10 xenografts was the induction of apoptosis 8 to 12 hours after a single dose of 60 mg/kg MLN4924, as evidenced by detection of cleaved caspase-3 [1]. A single dose of MLN4924 resulted in a dose- and time-dependent decrease of NEDD8-cullin levels as early as 30

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min after administration of MLN4924 (10, 30 or 60 mg/kg, subcutaneous), with maximal effect 1-2 h post-dose on HCT-116 tumour-bearing mice [2].

References:

- [1]. Milhollen M A, Traore T, Adams-Duffy J, et al. MLN4924, a NEDD8-activating enzyme inhibitor, is active in diffuse large B-cell lymphoma models: rationale for treatment of NF- κ B-dependent lymphoma[J]. Blood, The Journal of the American Society of Hematology, 2010, 116(9): 1515-1523.
- [2]. Soucy T A, Smith P G, Milhollen M A, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer[J]. Nature, 2009, 458(7239): 732-736.
- [3]. Nawrocki S T, Griffin P, Kelly K R, et al. MLN4924: a novel first-in-class inhibitor of NEDD8-activating enzyme for cancer therapy[J]. Expert opinion on investigational drugs, 2012, 21(10): 1563-1573.

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