

Product Data Sheet

Product Name: MLN2238

Cat. No.: GC16146

Chemical Properties

Cas. No. 1072833-77-2

Chemical Name [(1R)-1-[[[(2S,3R)-3-hydroxy-2-[(6-phenylpyridine-2-carbonyl)amino]butanoyl]amino]-3-methylbutyl]boronic acid

SMILES B(C(CC(C)C)NC(=O)CNC(=O)C1=C(C=CC(=C1)Cl)Cl)(O)O

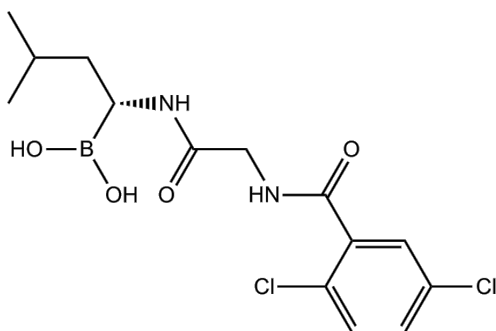
Formula $C_{14}H_{19}BCl_2N_2O_4$ M.Wt 361

Solubility ≥ 16.8 mg/mL in DMSO, ≥ 103 mg/mL in EtOH with ultrasonic 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

Kinase experiment [1]:

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Kinase assay

Calu-6 cells were cultured in MEM containing 10% fetal bovine serum and 1% Penicillin/Streptomycin and plated 1 day before the start of the experiment at 1×10^4 cells per well in a 384-well plate. Proteasome activity was assessed by monitoring hydrolysis of the chymotrypsin-like substrate Suc-LLVY-aminoluciferin in the presence of luciferase using the Proteasome-Glo assay reagents according to the manufacturer's instructions. Luminescence was measured using a LEADseeker instrument.

Cell experiment [1]:

Cell lines Calu-6 cells

Preparation method

The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reaction Conditions ≤ 10 nM; 1 hr

Applications MLN2238 inhibited Calu-6 cells with an IC_{50} value of 9.7 nM.

Animal experiment [2]:

Animal models DP54-Luc tumor-bearing NOD-SCID mice

Dosage form 11 mg/kg; i.v.; twice weekly for 17 consecutive days

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Applications	Both Bortezomib and MLN2238 reduced tumor burden (T/C = 0.48 and 0.22, respectively).
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

- [1]. Kupperman E, Lee EC, Cao Y, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Research*, 2010, 70 (5): 1970-80.
- [2]. Lee EC, Fitzgerald M, Bannerman B, et al. Antitumor Activity of the Investigational Proteasome Inhibitor MLN9708 in Mouse Models of B-cell and Plasma Cell Malignancies. *CLINICAL CANCER RESEARCH*, 2011, 17 (23): 7313-7323.

Background

MLN2238 is a potent reversible inhibitor that inhibits specific $\beta 5$ site of the 20S proteasome with IC50 value of 3.4 nM and Ki value of 0.93 nM.[1]

MLN2238, an N-capped dipeptidyl leucine boronic acid, preferentially bound to and inhibited the chymotrypsin-like proteolytic ($\beta 5$) site of the 20S proteasome with an IC50 value of 3.4 nM (Ki value of 0.93 nM). As the concentration increased, it also inhibited the caspase-like ($\beta 1$) with IC50 value of 31 nM and trypsin-like ($\beta 2$) proteolytic sites with IC50 value of 3,500 nM. The clinical studies in the model of both solid-tumor and hematological xenograft have demonstrated preclinical antitumor activity. Comparing to bortezomib, MLN2238 showed the activity in pharmacokinetics, pharmacodynamics and antitumor. It is believed that the activation of caspases, the p53 pathway, and endoplasmic reticulum stress and inhibition of NF- κ B are related to MLN2238-induced MM cell death. [1,2]

MLN2238 inhibited growth and triggers apoptosis in MM cells resistant to conventional and bortezomib therapies without affecting the viability of normal cells [2]. MLN2238 has significant cytotoxic activity in RSCL and RRCL preclinical models. Although BTZ and MLN2238 have similar

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reversible proteasome inhibition, the proteasome dissociation half-life ($t_{1/2}$) of MLN2238 was found to be approximately sixfold faster than BTZ ($t_{1/2}$ of 18 vs. 110min, respectively) while has the similar LD50 values to BTZ in a variety of cultured mammalian cancer cell lines. MLN2238 is approximately two to three times more potent than BTZ in lymphoma cell models. The IC50 of MLN2238 was 2.5 nmol/l in contrast to 7.5nmol/l of BTZ in Raji parental cells. [3]

In many mouse models of hematologic malignancies, such as tumor xenograft models which derived from a human lymphoma cell line and primary human lymphoma tissue, and genetically engineered mouse models of plasma cell malignancies, the result showed the antitumor activity of MLN2238.[4]

References:

- 1.Kupperman E, Lee EC, Cao Y, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Research*, 2010, 70 (5): 1970-80.
- 2.Tian Z, Zhao J, Tai Y, et al. Investigational agent MLN9708/2238 targets tumor-suppressor miR33b in MM cells. *Blood*, 2012, 120 (19): 3958-3967
- 3.Gu JJ, Hernandez-Ilizaliturri FJ, Mavis C, et al. MLN2238, a proteasome inhibitor, induces caspase-dependent cell death, cell cycle arrest, and potentiates the cytotoxic activity of chemotherapy agents in rituximab-chemotherapy-sensitive or rituximab-chemotherapy-resistant B-cell lymphoma preclinical models. *ANTI-CANCER DRUGS*, 2013, 24 (10): 1030-1038.
- 4.Lee EC, Fitzgerald M, Bannerman B, et al. Antitumor Activity of the Investigational Proteasome Inhibitor MLN9708 in Mouse Models of B-cell and Plasma Cell Malignancies. *CLINICAL CANCER RESEARCH*, 2011, 17 (23): 7313-7323.

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