Ixazomib

Cat. No.: HY-10453

CAS No.: 1072833-77-2

Molecular Formula: $C_{14}H_{19}BCl_2N_2O_4$

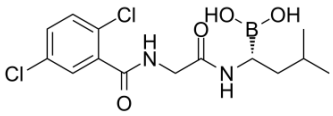
Molecular Weight: 361.03

Target: Proteasome; Autophagy

Pathway: Metabolic Enzyme/Protease; Autophagy

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 : ≥ 28 mg/mL (77.56 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.7699 mL	13.8493 mL	27.6985 mL
5 mM	0.5540 mL	2.7699 mL	5.5397 mL
10 mM	0.2770 mL	1.3849 mL	2.7699 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 (6.92 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.92 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.92 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Ixazomib (MLN2238) is a selective, potent, and reversible proteasome inhibitor, which inhibits the chymotrypsin-like proteolytic (β5) site of the 20S proteasome with an IC_{50} of 3.4 nM (K_i of 0.93 nM).

IC_{50} & Target

IC50: 3.4 nM (20S proteasome)[1]

Ki: 0.93 nM (20S proteasome)[1]

In Vitro	Ixazomib (MLN2238) is an N-capped dipeptidyl leucine boronic acid and preferentially bound to and inhibited the chymotrypsin-like proteolytic (β5) site of the 20S proteasome with an IC_{50} value of 3.4 nM (K_i of 0.93 nM). At higher concentrations, Ixazomib (MLN2238) also inhibits the caspase-like (β1) and trypsin-like (β2) proteolytic sites (IC_{50} of 31 and 3,500 nM, respectively). Cell viability studies are performed in a variety of mammalian cell lines to compare the in vitro antiproliferative effects of Ixazomib (MLN2238) with Bortezomib. Studies performed with A375 (lung), H460 (lung), HCT-116 (colon), and HT-29 (colon) cells revealed similar LD_{50} values for the two compounds, which range from 4 to 58 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Ixazomib (MLN2238) shows antitumor activity in the CWR22 xenograft model. The antitumor effects of Ixazomib (MLN2238) dosed at 14 mg/kg i.v. or 7 mg/kg i.v. are compared with Bortezomib dosed at 0.8 mg/kg i.v. or 0.4 mg/kg i.v. on a twice weekly regimen. The high dose for both Ixazomib (MLN2238) and Bortezomib shows similar antitumor activity in this model (T/C=0.36 and 0.44, respectively). However, Ixazomib (MLN2238) (7 mg/kg) shows greater efficacy at a 0.5 MTD dose compared with a 0.5 MTD dose of Bortezomib (0.4 mg/kg; T/C=0.49 compared with T/C=0.79, respectively) Ixazomib (MLN2238) shows time-dependent reversible proteasome inhibition; however, the proteasome dissociation half-life ($t_{1/2}$) for Ixazomib (MLN2238) is determined to be 18 minutes[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Calu-6 cells are cultured in MEM containing 10% fetal bovine serum and 1% penicillin/streptomycin and plated 1 d before the start of the experiment at 10,000 cells per well in a 384-well plate. For IC_{50} determinations, cells are treated with varying concentrations of Bortezomib or Ixazomib in DMSO (0.5% final, v/v) for 1 h at 37°C. For reversibility experiments, cells are treated with either 1 μM Bortezomib or Ixazomib (MLN2238) for 30 min at 37°C and then washed thrice in medium to remove the compounds. Cells are incubated for an additional 4 h at 37°C, after which the medium is removed and replaced with fresh medium. Proteasome activity is assessed by monitoring hydrolysis of the chymotrypsin-like substrate Suc-LLVY-aminoluciferin in the presence of luciferase using the Proteasome-Glo assay reagents. Luminescence is measured using a LEADseeker instrument[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Male CB17-SCID mice, approximately 8 to 11 wk of age, are inoculated s.c. with freshly dissected CWR22 tumor fragments (~20 mg) in the right dorsal flank. Mean tumor volume (MTV) is calculated using the following formula: 0.5×(length×width^2). When MTV reaches approximately 150 to 200 mm^3, animals are randomized into treatment groups (n=10 per group) before dosing. Antitumor activity is determined at the end of the study by calculating the treatment over control (T/C) ratio of their MTVs at the end of the study. Rats[1] To determine the pharmacokinetic profile of Ixazomib and Bortezomib in a second species, Sprague-Dawley rats are administered a single i.v. dose of Ixazomib (MLN2238) at either 0.3 or 0.2 mg/kg or Bortezomib at 0.2 mg/kg. Both Ixazomib doses provided a greater plasma exposure ($AUC_{0\text{-}48h}$ of 704 and 1,070 h•ng/mL for 0.2 and 0.3 mg/kg doses, respectively) compared with Bortezomib ($AUC_{0\text{-}48h}$ of 206 h•ng/mL), confirming that Ixazomib (MLN2238) also has improved plasma exposure compared with Bortezomib in rodents. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Blood. 2019 Jan 10;133(2):156-167.
- Elife. 2019 Mar 12;8:e44161.
- Amyloid. 2019 Mar;26(1):24-33.

- Oncotarget. 2020 Nov 3;11(44):3921-3932.

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REFERENCES

[1]. Kupperman E, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. Cancer Res. 2010 Mar 1;70(5):1970-80.

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