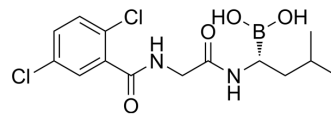


## Ixazomib

<b>Cat. No.:</b>	HY-10453		
<b>CAS No.:</b>	1072833-77-2		
<b>Molecular Formula:</b>	C <sub>14</sub> H <sub>19</sub> BCl <sub>2</sub> N <sub>2</sub> O <sub>4</sub>		
<b>Molecular Weight:</b>	361.03		
<b>Target:</b>	Proteasome; Autophagy		
<b>Pathway:</b>	Metabolic Enzyme/Protease; Autophagy		
<b>Storage:</b>	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



### SOLVENT & SOLUBILITY

#### In Vitro

DMSO : 62.5 mg/mL (173.12 mM; Need ultrasonic)

Concentration	Solvent	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	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

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline  
Solubility: ≥ 2.08 mg/mL (5.76 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)  
Solubility: ≥ 2.08 mg/mL (5.76 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil  
Solubility: ≥ 2.08 mg/mL (5.76 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<sub>50</sub> of 3.4 nM (K<sub>i</sub> of 0.93 nM).

#### IC<sub>50</sub> & Target

IC<sub>50</sub>: 3.4 nM (20S proteasome)<sup>[1]</sup>  
K<sub>i</sub>: 0.93 nM (20S proteasome)<sup>[1]</sup>

#### In Vitro

Ixazomib (MLN2238) is an N-capped dipeptidyl leucine boronic acid and preferentially bound to and inhibited the

chymotrypsin-like proteolytic ( $\beta 5$ ) 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 ( $\beta 1$ ) and trypsin-like ( $\beta 2$ ) 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<sup>[1]</sup>. 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 (HY-10227) 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<sup>[1]</sup>. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## PROTOCOL

#### Cell Assay<sup>[1]</sup>

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  $\mu$ M 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<sup>[1]</sup>.

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#### Animal Administration<sup>[1]</sup>

##### Mice<sup>[1]</sup>

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:  $0.5 \times (\text{length} \times \text{width}^2)$ . When MTV reaches approximately 150 to 200 mm<sup>3</sup>, 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<sup>[1]</sup>

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 ( $AUC_{0-48h}$  of 704 and 1,070 h•ng/mL for 0.2 and 0.3 mg/kg doses, respectively) compared with Bortezomib ( $AUC_{0-48h}$  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.
- Free Radic Biol Med. 2023 Apr 10;S0891-5849(23)00373-8.
- iScience. 19 July 2022, 104781.

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- Amyloid. 2019 Mar;26(1):24-33.

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## REFERENCES

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

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