产品名称：**B-[(1R)-1-[[2-[(2,5-二氯苯甲酰基)氨基]乙酰基]氨基]-3-甲基丁基]硼酸**
产品别名：**Ixazomib （MLN2238）；艾沙佐米**

生物活性：

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 (Ki 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].
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].
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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (6.92 mM); Clear solution

	此方案可获得 ≥ 2.5 mg/mL (6.92 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (6.92 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (6.92 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.92 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.92 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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].
Animal Administration	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: $0.5\times(length\times width^2)$. 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 ($AUC0\text{-}_{48h}$ of 704 and 1,070 h•ng/mL for 0.2 and 0.3 mg/kg doses, respectively) compared with Bortezomib ($AUC0\text{-}_{48h}$ of 206 h•ng/mL), confirming that Ixazomib (MLN2238) also has improved plasma exposure compared with Bortezomib in rodents.
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.

源叶生物