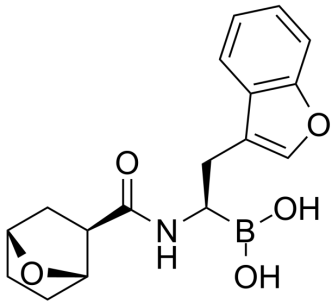
M3258

Cat. No.:	HY-111790
CAS No.:	2285330-15-4
Molecular Formula:	$C_{17}H_{20}BNO_5$
Molecular Weight:	329.16
Target:	Proteasome; Apoptosis
Pathway:	Metabolic Enzyme/Protease; Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (759.51 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.0380 mL	15.1902 mL	30.3804 mL
5 mM	0.6076 mL	3.0380 mL	6.0761 mL
10 mM	0.3038 mL	1.5190 mL	3.0380 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: ≥ 2.08 mg/mL (6.32 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (6.32 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (6.32 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

M3258 is an orally bioavailable, potent, reversible and highly selective immunoproteasome subunit LMP7 (β5i) inhibitor. M3258 exerts high biochemical (IC_{50}=3.6 nM) and cellular (IC_{50}=3.4 nM) potency against the LMP7 subunit. M3258 shows strong antitumor efficacy in multiple myeloma xenograft models. M3258 leads to a significant and prolonged suppression of tumor LMP7 activity and ubiquitinated protein turnover and the induction of apoptosis in multiple myeloma cells[1][2].

IC_{50} & Target

LMP7[1]

In Vitro

M3258 inhibits human LMP7 with a mean IC_{50} of 4.1 nM. M3258 displays weak activity against the constitutive proteasome subunit β5 (mean IC_{50}=2519 nM). M3258 potently inhibits LMP7 in the human multiple myeloma cell lines MM.1S and U266B1 and in human, rat, and dog PBMCs with IC_{50}s between 2 and 37 nM[2].

M3258 induces a >four fold accumulation of ubiquitinated proteins with an EC_{50} of 1980 nM in MM.1S cells. M3258 interferes with immunoproteasome function. M3258 also induces apoptosis assessed by caspase 3/7 activity (EC_{50}=420 nM;>3.5-fold induction) and reduces MM.1S cell viability (IC_{50}=367 nM)[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[2]

Cell Line:	MM.1S cells
Concentration:	0.01-100 nM
Incubation Time:	2 hours
Result:	Potently inhibited LMP7 in the human multiple myeloma cell lines MM.1S (IC_{50}=2.2 nM).

In Vivo

M3258 (1 mg/kg; 10 mg/kg) shows superior antitumor efficacy in selected multiple myeloma and mantle cell lymphoma xenograft models compared with the approved nonselective proteasome inhibitors bortezomib and ixazomib[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Female H2d Rag2 mice or female CB-17 SCID mice (U266B1 subcutaneous xenograft model; MM.1S subcutaneous xenograft model)[2]
Dosage:	1 mg/kg in U266B1 subcutaneous xenograft model; 10 mg/kg in MM.1S subcutaneous xenograft model
Administration:	P.o.; either once daily, every 2 days or twice weekly (days 1 and 4)
Result:	Displayed significant and strong antitumor efficacy.

CUSTOMER VALIDATION

- Cell Death Dis. 2022 Oct 8;13(10):860.

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REFERENCES

[1]. Klein M, et al. Structure-Based Optimization and Discovery of M3258, a Specific Inhibitor of the Immunoproteasome Subunit LMP7 (β5i) [published online ahead of print, 2021 Jul 6]. J Med Chem. 2021;10.1021/acs.jmedchem.1c00604.

[2]. Sanderson MP, et al. M3258 Is a Selective Inhibitor of the Immunoproteasome Subunit LMP7 (β5i) Delivering Efficacy in Multiple Myeloma Models [published online ahead of print, 2021 May 27]. Mol Cancer Ther. 2021;10.1158/1535-7163.MCT-21-0005.

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