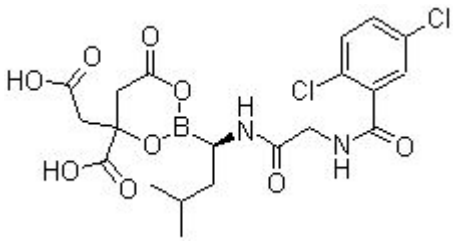
Product Introduction

MLN9708

MLN9708 immediately hydrolyzed to MLN2238, the biologically active form, on exposure to aqueous solutions or plasma. MLN2238 inhibits the chymotrypsin-like proteolytic (β5) site of the **20S proteasome** with **IC50/K_I** of 3.4 nM/0.93 nM, less potent to β1 and little activity to β2. Phase 3.

Technical Data:

Molecular Weight (MW):	517.12	
Formula:	$C_{20}H_{23}BCl_2N_2O_9$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 103 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1201902-80-8	

Biological Activity

MLN9708 is a selective, orally bioavailable, second-generation proteasome inhibitor. MLN9708 has a shorter proteasome dissociation half-life and improved pharmacokinetics, pharmacodynamics, and antitumor activity compared with bortezomib, which we believe plays an important role in its improved tissue distribution. MLN9708 has a larger blood volume distribution at steady state, and analysis of 20S proteasome inhibition and markers of the unfolded protein response confirms that MLN9708 has greater

pharmacodynamic effects in tissues than bortezomib. MLN9708 is a second-generation small-molecule proteasome inhibitor being developed for the treatment of a broad range of human malignancies. [1] Upon exposure to aqueous solutions or plasma, MLN9708 rapidly hydrolyzes to its biologically active form MLN2238. [2] MLN2238 is the biologically active form of MLN9708. [3]

MLN9708 shows superior antitumor activity in both solid tumor and hematologic preclinical xenograft models when administered via multiple dosing routes and regimens. [1] Recent preclinical pharmacology studies shows that MLN9708 has a shorter proteasome dissociation half-life than bortezomib, as well as improved pharmacokinetics, pharmacodynamics, and antitumor activity in xenograft models [2] MLN9708 has shown antitumor efficacy in a wide range of tumor xenografts. [4]

The 1st oral proteasome inhibitor in early stage clinical trials for Multiple Myeloma.

References

[1] Kupperman E, et al. Cancer Res, 2010, 70(5), 1970-80.

[2] Chauhan D, et al. Clin Cancer Res, 2011, 17(16), 5311-21.

[3] Lee EC, et al.Clin Cancer Res, 2011, 17(23),7313-23.

[4] E. T. Rodler, et al. Journal of Clinical Oncology, 2010, 28(15)

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