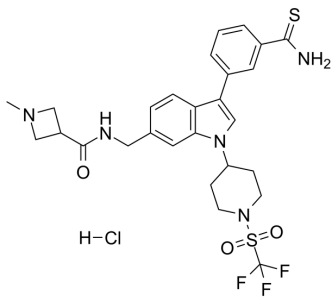
AS-99

Cat. No.:	HY-141429C
Molecular Formula:	$C_{27}H_{31}ClF_3N_5O_3S_2$
Molecular Weight:	630.14
Target:	Histone Methyltransferase; Apoptosis
Pathway:	Epigenetics; Apoptosis
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	AS-99 is a first-in-class, potent, and selective ASH1L histone methyltransferase inhibitor (IC_{50}= 0.79 μM, K_d= 0.89 μM) with anti-leukemic activity. AS-99 blocks cell proliferation, induces apoptosis and differentiation, downregulates MLL fusion target genes, and reduces the leukemia burden in vivo[1].
IC_{50} & Target	0.79 μM (ASH1L histone methyltransferase)[1]
In Vitro	AS-99 is tested against a panel of 20 histone methyltransferases, including NSD1, NSD2, NSD3, and SETD2. NO significant inhibition is observed at 50 μM of AS-99 on any of the tested histone methyltransferases, indicating over 100-fold selectivity towards ASH1L[1]. AS-99 shows a several fold weaker effect on the proliferation of leukemia cells without MLL1 translocations, such as SET2 and K562, with no or limited effects at 10 μM or higher concentrations[1]. AS-99 (1-8 μM; 7 days) also induces apoptosis in the MLL leukemia cells, but not in the K562 cells, as assessed by the quantification of the Annexin V positive cells[1]. AS-99 suppresses MLL fusion driven transcriptional programs[1]. AS-99 results in a reduced number of H3K36me2 peaks when compared to the DMSO-treated cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AS-99 (30 mg/kg; i.p.; q.d., treated for 14 consecutive days) reduces leukemia burden in mice[1]. AS-99 is used for in vivo studies in mice, which reveals favorable exposure in plasma upon i.v. and i.p. administration (AUC = 9701 hr* ng/mL and 10,699 hr* ng/mL, respectively), suitable half-life (~5-6 h) and C_{max} > 10 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

RT-PCR[1]

Cell Line:	MOLM13 cells
Concentration:	2-6 μM
Incubation Time:	7 days
Result:	Led to a dose-dependent downregulation of canonical MLL fusion target genes required for leukemogenesis including MEF2C, DLX2, FLT3, and HOXA9.

Animal Model:	8- to 10-week old female NSG mice (bearing MV4;11 cells)[1]
Dosage:	30 mg/kg
Administration:	I.p.; q.d., treated for 14 consecutive days
Result:	Reduced the leukemia burden in the xenotransplantation mouse model of MLL leukemia without affecting blood counts in normal mice.

REFERENCES

[1]. Rogawski DS, et al. Discovery of first-in-class inhibitors of ASH1L histone methyltransferase with anti-leukemic activity. Nat Commun. 2021 May 14;12(1):2792.

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