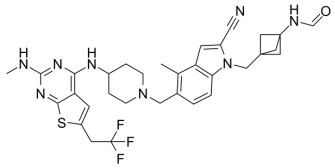
MI-3454

Cat. No.:	HY-136360
CAS No.:	2134169-43-8
Molecular Formula:	$C_{32}H_{35}F_3N_8OS$
Molecular Weight:	637
Target:	Epigenetic Reader Domain
Pathway:	Epigenetics
Storage:	4°C, stored under nitrogen * In solvent : -80°C, 2 years; -20°C, 1 year (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 31.25 mg/mL (49.06 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.5699 mL	7.8493 mL	15.6986 mL
	5 mM	0.3140 mL	1.5699 mL	3.1397 mL
	10 mM	0.1570 mL	0.7849 mL	1.5699 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 20% HP-β-CD >> 5% Cremophor EL
   Solubility: 5 mg/mL (7.85 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

MI-3454 is an orally active, highly potent and selective menin-MLL1 interaction inhibitor with an IC_{50} of 0.51 nM. MI-3454 inhibits proliferation, induces differentiation and complete remission or regression of leukemia in mouse models of MLL1-rearranged or NPM1-mutated leukemia through downregulation of key genes involved in leukemogenesis[1].

IC_{50} & Target

IC50: 0.51 nM (menin-MLL1 interaction)[1]

In Vitro

MI-3454 (0.001-10 μM; 7 days) strongly reduces murine bone marrow cells transformed with MLL-AF9 or Hoxa9/Meis1 proliferation[1].

MI-3454 (50 nM; 6 days) leads to downregulated expression of HOXA9 and MEIS1 in Human leukemic cell lines MV-4-11 cells or MOLM13[1].

MI-3454 markedly reduces the viability of leukemic cells harboring various MLL fusion proteins (MLL-AF9, MLL-AF4, MLL-ENL), with GI_{50} values ranging from 7 to 27 nM. MI-3454 blocks the interaction of menin with an $MLL1_{4-43}$ fragment encompassing the entire menin binding motif[1].

MI-3454 does not potently inhibit cytochromes P450 (<50% inhibition at 10 μM)[1].

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

Cell Proliferation Assay[1]

Cell Line:	Murine bone marrow cells transformed with MLL-AF9 or Hoxa9/Meis1
Concentration:	0.001, 0.01, 0.1, 1, 10 μM
Incubation Time:	7 days
Result:	Demonstrated strong reduction of cell proliferation.

RT-PCR[1]

Cell Line:	Human leukemic cell lines MV-4-11 cells or MOLM13
Concentration:	50 nM
Incubation Time:	6 days
Result:	Led to downregulated expression of HOXA9 and MEIS1 and expression level of other MLL fusion target genes, including MEF2C, DLX2, HOXA10, PBX3, and FLT3.

In Vivo

MI-3454 induces complete remission or regression of leukemia in mouse models of mixed lineage leukemia 1 (MLL1)-rearranged or nucleophosmin 1 (NPM1)-mutated leukemia[1].

MI-3454 (p.o.; 120 mg/kg; one or twice daily for 7 consecutive days) sufficiently blocks leukemia progression by a once-daily treatment[1].

MI-3454 (p.o.; 100 mg/kg; b.i.d.; for 19 consecutive days) effectively blocks leukemia progression during the treatment period and markedly prolongs survival of MOLM13 xenotransplantation model mice. MI-3454 induces complete remission or blocks leukemia progression in patient-derived xenograft (PDX) models of MLL leukemia[1].

MI-3454 (100 mg/kg of PO or 15 mg/kg of IV) has a $T_{1/2}$ of 3.2 hours, a C_{max} of 4698 mg/mL for PO[1].

MI-3454 exhibits favorable stability in murine and human liver microsomes ($t_{1/2}$=20.4 minutes and 37.1 minutes, respectively)[1].

MI-3454 demonstrates lower levels in brain and cerebrospinal fluid, suggesting limited ability to cross the blood-brain barrier[1].

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

Animal Model:	8- to 10-week-old female NSG mice (MV-4-11 xenotransplantation model of MLL leukemia)[1]
Dosage:	120 mg/kg
Administration:	Orally; one or twice daily for 7 consecutive days
Result:	A once-daily treatment was sufficient to block leukemia progression.

Animal Model:	Female CD-1 mice[1]
Dosage:	100 mg/kg (PO) or 15 mg/kg (IV) (Pharmacokinetic Analysis)
Administration:	PO or IV
Result:	Had a $T_{1/2}$ of 3.2 hours, a C_{max} of 4698 mg/mL for PO. Had a $T_{1/2}$ of 2.4 hours, a CL of 2375 mL/hours•kg, and a V_{ss} of 5358 mL/kg for IV.

CUSTOMER VALIDATION

- iScience. 2021 Dec 25;25(1):103679.

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REFERENCES

[1]. Szymon Klossowski, et al. Menin Inhibitor MI-3454 Induces Remission in MLL1-rearranged and NPM1-mutated Models of Leukemia. J Clin Invest. 2020 Feb 3;130(2):981-997.

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

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA