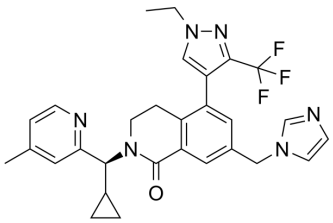
WDR5-IN-5

Cat. No.:	HY-150654
CAS No.:	2417012-26-9
Molecular Formula:	$C_{29}H_{29}F_3N_6O$
Molecular Weight:	534.58
Target:	Histone Methyltransferase
Pathway:	Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (187.06 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8706 mL	9.3531 mL	18.7063 mL
	5 mM	0.3741 mL	1.8706 mL	3.7413 mL
	10 mM	0.1871 mL	0.9353 mL	1.8706 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: 2.5 mg/mL (4.68 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 2.5 mg/mL (4.68 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

WDR5-IN-5 is an orally active and selective inhibitor of WIN site of WD repeat domain 5 (WDR5). WDR5-IN-5 exhibits anti-proliferative activity towards cancer cells and good pharmacokinetics profile in mice. WDR5-IN-5 shows high affinity to WDR5 and the binding affinity K_i value <0.02 nM[1].

IC_{50} & Target

Target: WIN site of WD repeat domain 5 (WDR5)[1]

In Vitro

WDR5 plays an important role in the activity of MLL1 histone methyltransferase (HMT) complexes. WDR5-IN-5 (compound 41), as a WDR5 inhibitor, will exihibits inhibitory effect towards HMT[1].
WDR5-IN-5 displays average soluble concentrations (kinetic solubility) of 60 μM[1].
WDR5-IN-5 exhibits high selectivity between K562 cells and MV4:11, the selectivity index ($GI_{50,\ K562}/GI_{50,\ MV4:11}$) is 290[1].

WDR5-IN-5 (0-30 μM; 5 d) inhibits cell proliferation of MV4:11, MOLM-13, and K562 with GI_{50} values are 13, 27, 3700 nM, respectively[1].

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

Cell Proliferation Assay[1]

Cell Line:	MV4:11, MOLM-13 cells
Concentration:	0-30 μM
Incubation Time:	5 days
Result:	Inhibited cell growth of MV4:11, MOLM-13, and showed on- and off-target inhibition mechanism.

In Vivo

WDR5-IN-5 (compound 41) (10 mg/kg; p.o.) shows high oral exposure ($AUC_{0,inf}$=3984 h·ng/mL), long half-life of $T_{1/2}$=1.3 h[1]. WDR5-IN-5 (3 mg/kg; i.v.) also shows low iv clearance (26 mL/min/kg). WDR5-IN-5 is well tolerated and shows no adverse effects in mice by both i.v. and p.o. dosing[1].

WDR5-IN-5 can be formulated as 0.6 and 1 mg/mL solutions in ethanol, tocopherol poly (ethylene glycol) succinate (TPGS), PEG400 and water (v/v/v/v, 5/5/30/60) for i.v. and p.o. dosing, respectively[1].

PK profile of WDR5-IN-5 in CD-1 Mice[1]

Route	Dose (mg/kg)	CL (mL/min/kg)	$AUC_{0,inf}$ (h·ng/mL)	V_{ss} (L/kg)	$T_{1/2}$ (h)	*F* (%)
i.v.	3	26	1951	1.6	/	/
p.o.	10	2083	3984	/	1.3	61

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Animal Model:	Male CD-1 mice[1]
Dosage:	3 mg/kg i.v.; 10 mg/kg p.o.
Administration:	Intravenous injection or oral gavage
Result:	Showed high oral exposure ($AUC_{0,inf}$=3984 h.ng/mL), long half-life of $T_{1/2}$=1.3 h, and low iv clearance (26 mL/min/kg).

REFERENCES

[1]. Teuscher KB, et al. Discovery of Potent Orally Bioavailable WD Repeat Domain 5 (WDR5) Inhibitors Using a Pharmacophore-Based Optimization. J Med Chem. 2022 Apr 28. 65(8):6287-6312.

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