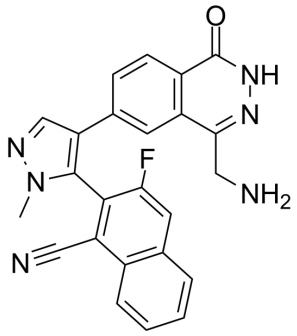
MRTX9768

Cat. No.:	HY-138684
CAS No.:	2629314-68-5
Molecular Formula:	$C_{24}H_{17}FN_6O$
Molecular Weight:	424.43
Target:	Histone Methyltransferase
Pathway:	Epigenetics
Storage:	-20°C, protect from light * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (117.81 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3561 mL	11.7805 mL	23.5610 mL
	5 mM	0.4712 mL	2.3561 mL	4.7122 mL
	10 mM	0.2356 mL	1.1781 mL	2.3561 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 (5.89 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.89 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.89 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MRTX9768 is a potent, selective, orally active, first-in-class PRMT5-MTA complex inhibitor[1].

IC_{50} & Target

PRMT5

In Vitro

MRTX9768 inhibits SDMA and cell proliferation in HCT116 MTAP-del cells (SDMA IC_{50} 3 nM; prolif. IC_{50} 11 nM) with marked selectivity over HCT116 MTAP-WT cells (SDMA IC_{50} 544 nM; prolif. IC_{50} 861 nM)[1].
?MRTX9768 (0-250 nM) results in LU99 SDMA inhibition maintaining after 3-hr drug treatment followed by 4-day washout (exhibiting tight binding and prolonged PRMT5?MTA occupancy)[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	In xenograft studies, oral administration of MRTX9768 demonstrates dose-dependent inhibition of SDMA in MTAP-del tumors, with less SDMA modulation observed in bone marrow[1]. ?MRTX9768 selectively targets MTAP/CDKN2A-deleted tumors (such as glioblastoma)[1][2]. ?MRTX9768 (PO dose 30 mg/kg in CD-1 mouse and beagle dog, 10 mg/kg in cynomolgus monkey) has a favorable ADME profile (>50% bioavailability in mice and dogs, moderate to high clearance, No changes in RBC parameters when administered well above efficacious concentrations (1000 mg/kg))[3]. ?MRTX9768 (100 mg/kg, orally, BID, 6/21 days) results in SDMA inhibition maintaining 3 days after dosing is stopped[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Christopher R. et al. Fragment based discovery of MRTX9768, a synthetic lethal-based inhibitor designed to bind the PRMT5-MTA complex and selectively target MTAP/CDKN2A-deleted tumors [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2021; 2021 Apr 10-15 and May 17-21. Philadelphia (PA): AACR; Cancer Res 2021;81(13_Suppl):Abstract nr LB003.

[2]. Yingqing Chen, et al. Targeting protein arginine methyltransferase 5 in cancers: Roles, inhibitors and mechanisms. Biomed Pharmacother. 2021 Oct 4;144:112252.

[3]. Matthew A. Marx, et al. Fragment-based discovery of MRTX9768, a synthetic lethal- based inhibitor designed to bind the PRMT5•MTA complex and selectively target MTAPDEL tumors. AACR ANNUAL MEETING 2021:APRIL 10-15, 2021 AND MAY 17-21, 2021.

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