MRTX1133

Cat. No.: HY-134813

CAS No.: 2621928-55-8

Molecular Formula: $C_{33}H_{31}F_3N_6O_2$

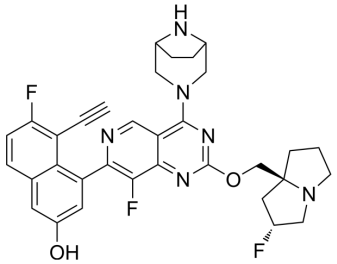
Molecular Weight: 600.63

Target: Ras

Pathway: GPCR/G Protein; MAPK/ERK Pathway

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 : 50 mg/mL (83.25 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6649 mL	8.3246 mL	16.6492 mL
	5 mM	0.3330 mL	1.6649 mL	3.3298 mL
	10 mM	0.1665 mL	0.8325 mL	1.6649 mL

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

In Vivo

1. Add each solvent one by one: 10% SBE-β-CD/50 mM citrate pH 5.0
   Solubility: 10 mg/mL (16.65 mM); Clear solution; Need ultrasonic and warming and adjust pH to 5 with HCl and heat to 60°C
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 3.5 mg/mL (5.83 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.16 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MRTX1133 is a noncovalent, potent, and selective KRAS G12D inhibitor. MRTX1133 optimally fills the switch II pocket and extends three substituents to favorably interact with the protein, resulting in an estimated K_D against KRAS G12D of 0.2 pM. MRTX1133 prevents SOS1-catalyzed nucleotide exchange and/or formation of the KRAS G12D/GTP/RAF1 complex, thereby inhibiting mutant KRAS-dependent signal transduction. MRTX1133 selectively inhibits KRAS G12D mutant, but not KRAS wild-type, tumor cells. MRTX1133 has single digit nanomolar activity in cellular assays and marked in vivo efficacy in tumor models harboring KRAS G12D mutations[1][2].

IC_{50} & Target	KRas G12D 0.2 pM (Kd)
In Vitro	MRTX1133 inhibits ERK phosphorylation in the AGS cell line with an IC_{50} ranging 1-10 nM (AsPC-1, Panc 04.03, Panc 02.03, SW1990, GP2D, Suit2, A427, SNU1033, and HPAC cells). In a 2D viability assay, the IC_{50} of MRTX1133 is 6 nM against AGS cells (KRAS G12D), while demonstrating more than 500-fold selectivity against MKN1, a cell line which is dependent on KRAS for its growth and survival due to the amplification of wild-type KRAS[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	MRTX1133 displays efficacious in a KRAS G12D mutant xenograft mouse tumor model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	6-8-weekold, female, athymic nude-Foxn1^{nu} mice (Panc 04.03 model)[1]
Dosage:	3, 10, or 30 mg/kg
Administration:	Intraperitoneal; twice a day for 28 days
Result:	An antitumor efficacy study in this model resulted in MRTX1133 dose-dependent antitumor activity with 94% growth inhibition observed at 3 mg/kg BID (IP) and tumor regressions of -62% and -73% observed at 10 and 30 mg/kg BID (IP), respectively.

CUSTOMER VALIDATION

- Immunity. 2023 Nov 14;56(11):2570-2583.e6.
- bioRxiv. 2023 Oct 6.
- bioRxiv. 2023 Sep 17.

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REFERENCES

[1]. Wang X, et al. Identification of MRTX1133, a Noncovalent, Potent, and Selective KRAS G12D Inhibitor [published online ahead of print, 2021 Dec 10]. J Med Chem. 2021;10.1021/acs.jmedchem.1c01688.

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