MRTX849

Cat. No.: HY-130149

CAS No.: 2326521-71-3

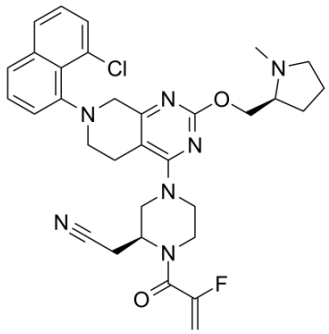
Molecular Formula: $C_{32}H_{35}ClFN_7O_2$

Molecular Weight: 604.12

Target: Ras

Pathway: GPCR/G Protein

Storage: -20°C, stored under nitrogen
* In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (41.38 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6553 mL	8.2765 mL	16.5530 mL
	5 mM	0.3311 mL	1.6553 mL	3.3106 mL
	10 mM	0.1655 mL	0.8277 mL	1.6553 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 (4.14 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.14 mM); Clear solution
3. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.62 mg/mL (4.34 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MRTX849 is a potent, orally-available, and mutation-selective covalent inhibitor of KRAS G12C with potential antineoplastic activity. MRTX849 covalently binds to KRAS G12C at the cysteine at residue 12, locks the protein in its inactive GDP-bound conformation, and inhibits KRAS-dependent signal transduction[1][2].

IC_{50} & Target

KRas G12C

In Vitro

MRTX849 (0.1-10000 nM; 3-day/2D conditions; 12-day/3D conditions) potently inhibits cell growth in the vast majority of KRAS G12C-mutant cell lines with IC_{50}s ranging between 10 and 973 nM in the 2D format and between 0.2 and 1042 nM in the 3D format[1].

MRTX849 (0.24-1000 nM; 24 hours) inhibits KRAS-dependent signaling targets including ERK1/2 phosphorylation (Thr202/Tyr204 ERK1; pERK), S6 phosphorylation (RSK-dependent Ser235/236; pS6) and expression of the ERK-regulated DUSP6[1].

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

Cell Viability Assay[1]

Cell Line:	MIA PaCa-2, H1373, H358, H2122, SW1573, H2030, KYSE-410 cells (G12C); H1299 (WT); A549 (G12S), HCT116 (G13D) cells
Concentration:	0.1, 1, 10, 100, 1000, 10000 nM
Incubation Time:	24 hours
Result:	Inhibits cell growth in the vast majority of KRAS G12C-mutant cell lines with IC_{50} values ranging between 10 and 973 nM in the 2D format and between 0.2 and 1042 nM in the 3D format.

Western Blot Analysis[1]

Cell Line:	MIA PaCa-2 cells
Concentration:	0.24, 0.5, 1.0, 2.0, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, 500, 1000 nM
Incubation Time:	24 hours
Result:	Inhibits KRAS-dependent signaling targets including ERK1/2 phosphorylation (Thr202/Tyr204 ERK1; pERK), S6 phosphorylation (RSK-dependent Ser235/236; pS6) and expression of the ERK-regulated DUSP6, each with IC_{50}s in the single-digit nanomolar range in cell lines.

In Vivo

MRTX849 (1-100 mg/kg; i.g.; daily until day 16) demonstrates dose-dependent anti-tumor efficacy over a well-tolerated dose range, and the maximally efficacious dose of MRTX849 is between 30-100 mg/kg/day[1].

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Animal Model:	MIA PaCa-2 model (6-8-week-old, female, athymic nude-Foxn1 nu mice)[1]
Dosage:	1, 3, 10, 30 and 100 mg/kg
Administration:	Oral gavage; daily until Day 16
Result:	Rapid tumor regression was observed at the earliest posttreatment tumor measurement and animals in the 30 and 100 mg/kg cohorts exhibited evidence of a complete response at study Day 15. Dosing was stopped at study Day 16 and all 4 mice in the 100 mg/kg cohort and 2 out of 7 mice in the 30 mg/kg cohort remained tumor-free through study Day 70.

REFERENCES

[1]. Christensen JG, et al. The KRASG12C Inhibitor, MRTX849, Provides Insight Toward Therapeutic Susceptibility of KRAS Mutant Cancers in Mouse Models and Patients. Cancer Discov. 2019 Oct 28. pii: CD-19-1167.

[2]. Kyriakos P. Papadopoulos, et al. A phase I/II multiple expansion cohort trial of MRTX849 in patients with advanced solid tumors with KRAS G12C mutation. Journal of Clinical Oncology 2019 37:15_suppl, TPS3161-TPS3161.

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

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