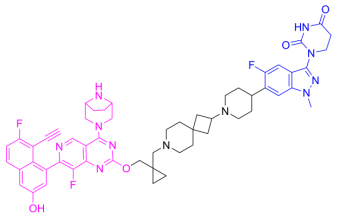
RP03707

Cat. No.:	HY-176134
CAS No.:	3030493-05-8
Molecular Formula:	$C_{55}H_{58}F_3N_{11}O_4$
Molecular Weight:	994.12
Target:	PROTACs; Ras
Pathway:	PROTAC; 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 : 100 mg/mL (100.59 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.0059 mL	5.0296 mL	10.0591 mL
	5 mM	0.2012 mL	1.0059 mL	2.0118 mL
	10 mM	0.1006 mL	0.5030 mL	1.0059 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 5 mg/mL (5.03 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

RP03707 is a PROTAC degrader of $KRAS^{G12D}$. RP03707 forms a ternary complex with $KRAS^{G12D}$ and the CRBN E3 ligase, promoting the ubiquitination and proteasomal degradation of $KRAS^{G12D}$. RP03707 inhibits the growth of $KRAS^{G12D}$-positive tumor cells[1].

In Vitro

RP03707 (0.0025-50 nM; 0-72 h) potently and rapidly degrades $KRAS^{G12D}$ protein in AsPC-1 cells, with a DC_{50} of 0.6 nM and sustained degradation for up to 36 h at 1 and 10 nM[1].

RP03707 (increasing concentrations; 24 h) potently degrades $KRAS^{G12D}$ protein in GP2D, PK-59, and AGS cells, with DC_{50} values ranging from 0.7 to 1.3 nM and high maximal degradation (82.0-96.0%)[1].

RP03707 (increasing concentrations; 24 h) potently inhibits ERK phosphorylation in AsPC-1, AGS, GP2D, and PK-59 cells, with IC_{50} values ranging from 0.35 to 10.6 nM[1].

RP03707 (increasing concentrations; 72 h) potently inhibits proliferation of AsPC-1, AGS, GP2D, and PK-59 cells, with IC_{50} values ranging from 0.19 to 4.19 nM[1].

RP03707 (1 μM; 0-120 min) exhibits favorable metabolic stability across multiple species, with exceptionally long human plasma stability and moderate human liver clearance[1].

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

Western Blot Analysis[1]

Cell Line:	human pancreatic cancer AsPC-1 cells
Concentration:	5 nM (screening); 0.0025-50 nM (24 h dose-response); 1-10 nM (time-course)
Incubation Time:	24 h (dose-response); 0, 1, 3, 6, 12, 24, 36, 48, 72 h (time-course)
Result:	Induced over 90% $KRAS^{G12D}$ degradation at 5 nM. Achieved a DC_{50} of 0.6 nM and a maximal degradation (D_{max}) of 89.0% in 24 h dose-response assay. Achieved ~70% maximal degradation at 12 h, which persisted until 36 h before declining at 1 nM. Achieved ~90% maximal degradation at 12 h, which persisted until 36 h with a slower decline through 72 h at 10 nM.

Western Blot Analysis[1]

Cell Line:	human colon cancer GP2D cells, human pancreatic cancer PK-59 cells, human gastric cancer AGS cells
Concentration:	increasing concentrations (dose-response analysis)
Incubation Time:	24 h
Result:	Exhibited a DC_{50} of 0.7 nM and a D_{max} of 93.3% in GP2D cells. Exhibited a DC_{50} of 0.7 nM and a D_{max} of 96.0% in PK-59 cells. Exhibited a DC_{50} of 1.3 nM and a D_{max} of 82.0% in AGS cells.

Cell Proliferation Assay[1]

Cell Line:	human pancreatic cancer AsPC-1 cells, human gastric cancer AGS cells, human colon cancer GP2D cells, human pancreatic cancer PK-59 cells
Concentration:	increasing concentrations
Incubation Time:	72 h
Result:	Inhibited cell proliferation with an IC_{50} of 4.19 nM in AsPC-1 cells. Inhibited cell proliferation with an IC_{50} of 1.01 nM in AGS cells. Inhibited cell proliferation with an IC_{50} of 0.19 nM in GP2D cells. Inhibited cell proliferation with an IC_{50} of 2.8 nM in PK-59 cells.

In Vivo

RP03707 (0.1-1 mg/kg; i.v.; weekly; 4 weeks) administered weekly via intravenous injection induces potent dose-dependent tumor growth inhibition in PK-59 $KRAS^{G12D}$ pancreatic cancer xenografts, with 98% TGI achieved at the 1 mg/kg dose[1].

RP03707 (1-10 mg/kg; i.v.; weekly, every 2 weeks; 4 weeks) administered via intravenous injection induces dose-dependent tumor growth inhibition and regression in GP2D $KRAS^{G12D}$ colorectal cancer xenografts, with 30.9% tumor regression achieved at the 10 mg/kg weekly dose[1].

RP03707 (10 mg/kg; i.v.; single dose) achieves sustained high tumor concentrations, prolonged $KRAS^{G12D}$ degradation, suppressed MAPK signaling, and increased apoptotic markers in PK-59 $KRAS^{G12D}$ pancreatic cancer xenografts for up to 168 hours[1].

RP03707 (10 mg/kg; i.v.; single dose) achieves high, sustained tumor concentrations, 95% $KRAS^{G12D}$ degradation, suppressed MAPK signaling, and increased apoptotic markers in GP2D $KRAS^{G12D}$ colorectal cancer xenografts for up to 168

hours[1].

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

Animal Model:	BALB/c nude (female, 6–8 weeks old)[1]
Dosage:	0.1 mg/kg; 0.3 mg/kg; 1 mg/kg
Administration:	i.v.; weekly; 4 weeks
Result:	Achieved 81.4% tumor growth inhibition (TGI) at day 28 with 0.1 mg/kg dose. Achieved 93% TGI at day 28 with 0.3 mg/kg dose. Achieved 98% TGI at day 28 with 1 mg/kg dose. Showed no adverse effects based on body weight changes.

Animal Model:	BALB/c nude (female, 6–8 weeks old, tumor size ~500–700 mm^3)[1]
Dosage:	10 mg/kg
Administration:	i.v.; single dose
Result:	Maintained high tumor concentrations, decreasing from 1044 ng/g at 6 hours to 719 ng/g at 168 hours. Reached and maintained high levels of $KRAS^{G12D}$ protein degradation, with 87.7% degradation at 168 hours. Kept pERK levels consistently low. Reduced DUSP4 levels to 11% at 6 hours and maintained at 6.1% at 168 hours.

REFERENCES

[1]. Ji X, et al. Discovery and Characterization of RP03707: A Highly Potent and Selective $KRAS^{G12D}$ PROTAC. J Med Chem. 2025;68(10):10238-10254.

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