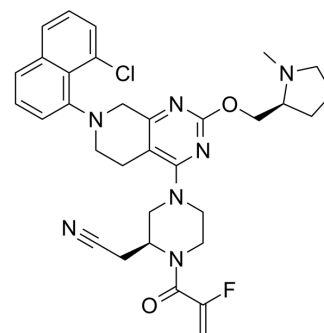


## Adagrasib

<b>Cat. No.:</b>	HY-130149		
<b>CAS No.:</b>	2326521-71-3		
<b>Molecular Formula:</b>	C <sub>32</sub> H <sub>35</sub> ClFN <sub>7</sub> O <sub>2</sub>		
<b>Molecular Weight:</b>	604		
<b>Target:</b>	Ras		
<b>Pathway:</b>	GPCR/G Protein; MAPK/ERK Pathway		
<b>Storage:</b>	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



### SOLVENT & SOLUBILITY

#### In Vitro

DMSO : 25 mg/mL (41.39 mM); ultrasonic and warming and heat to 60°C)

Concentration	Solvent	Mass	1 mg	5 mg	10 mg
			1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM		1.6556 mL	8.2781 mL	16.5563 mL
	5 mM		0.3311 mL	1.6556 mL	3.3113 mL
	10 mM		0.1656 mL	0.8278 mL	1.6556 mL

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

#### In Vivo

- 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
- 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
- Add each solvent one by one: 10% DMSO >> 90% corn oil  
Solubility: ≥ 2.5 mg/mL (4.14 mM); Clear solution

### BIOLOGICAL ACTIVITY

#### Description

Adagrasib (MRTX849) is a potent, orally-available, and mutation-selective covalent inhibitor of KRAS G12C with potential antineoplastic activity. Adagrasib 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<sup>[1][2]</sup>.

#### IC<sub>50</sub> & Target

KRas G12C

#### In Vitro

Adagrasib (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<sub>50</sub>s ranging between 10 and 973 nM in the 2D format and between 0.2 and 1042 nM in the 3D format<sup>[1]</sup>.

Adagrasib (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<sup>[1]</sup>.

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

#### Cell Viability Assay<sup>[1]</sup>

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 <sub>50</sub> 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<sup>[1]</sup>

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 <sub>50</sub> s in the single-digit nanomolar range in cell lines.

#### In Vivo

Adagrasib (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<sup>[1]</sup>.

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

Animal Model:	MIA PaCa-2 model (6-8-week-old, female, athymic nude-Foxn1 nu mice) <sup>[1]</sup>
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.

#### CUSTOMER VALIDATION

- Nature. 2023 Apr;616(7957):563-573.
- Cancer Cell. 2023 Sep 11;41(9):1606-1620.e8.
- Nat Cancer. 2023 Jun;4(6):829-843.

- J Thorac Oncol. 2021 May 7;S1556-0864(21)02132-8.
- Nat Commun. 2023 Oct 10;14(1):6332.

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## REFERENCES

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[1]. Fell JB, Fischer JP, Baer BR, et al. Identification of the Clinical Development Candidate MRTX849, a Covalent KRASG12C Inhibitor for the Treatment of Cancer. J Med Chem. 2020;63(13):6679-6693.

[2]. Awad MM, Liu S, Rybkin II, et al. Acquired Resistance to KRASG12C Inhibition in Cancer. N Engl J Med. 2021;384(25):2382-2393.

[3]. 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.

[4]. 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.

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

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