上海源叶生物科技有限公司
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产品名称：MRTX-849 ；Adagrasib

CAS 号：2326521-71-3

产品货号：S88622

生物活性：

Description	Adagrasib (MRTX849) 是一种有效，口服可用，突变选择性的 KRAS G12C 共价抑制剂，具有潜在抗肿瘤活性的。Adagrasib 在半胱氨酸 12 残基处与 KRAS G12C 共价结合，将蛋白锁定在非活性的 GDP 结合构象中，并抑制 KRAS 依赖性信号转导。
IC50 & Target	KRas G12C

Cellular Effect

Cell Line	Type	Value	Description
A549	IC_{50}	12.9 μM	Antiproliferative activity against human A549 cells harboring KRAS G12S mutant assessed as inhibition of cell proliferation incubated for 3 days by CCK8 assay
AGS	IC_{50}	1.4 μM	Antiproliferative activity against human AGS cells assessed as reduction in cell viability measured after 3 days by Celltiter-Glo assay
MIA PaCa-2	IC_{50}	0.05 μM	Antiproliferative activity against human MIA PaCa-2 cells harboring KRAS G12C mutant assessed as inhibition of cell proliferation incubated for 3 days by CCK8 assay
MIA PaCa-2	IC_{50}	0.1 μM	Antiproliferative activity against human MIA PaCa-2 cells
MIA PaCa-2	IC_{50}	3.92 nM	Antiproliferative activity against human MIA PaCa-2 cells assessed as inhibition of cell growth incubated for 72 hrs by cell count reagent SF based assay
MIA PaCa-2	IC_{50}	4 nM	Antiproliferative activity against human MIA PaCa-2 cells assessed as reduction in cell viability measured after 3 days by Celltiter-Glo assay
MIA PaCa-2	IC_{50}	5 nM	Inhibition of KRAS G12C mutant in human MIAPaCa2 cells assessed as reduction in ERK phosphorylation incubated for 24 hrs by in-cell western method
NCI-H1975	IC_{50}	6.37 μM	Antiproliferative activity against human NCI-H1975 cells harboring wild-type KRAS assessed as inhibition of cell proliferation incubated for 3 days by CCK8 assay
NCI-H358	IC_{50}	0.001 μM	Antiproliferative activity against human NCI-H358 cells harboring KRAS G12C mutant assessed as inhibition of cell growth
NCI-H358	IC_{50}	0.006 μM	Antiproliferative activity against human NCI-H358 cells harboring KRAS G12C mutant cultured as 3D spheroids assessed as reduction in cell proliferation incubated for 3 days by CellTiter-Glo 3D reagent based assay
NCI-H358	IC_{50}	0.02 μM	Antiproliferative activity against human NCI-H358 cells harboring KRAS G12C mutant assessed as inhibition of cell proliferation incubated for 3 days by CCK8 assay
NCI-H358	IC_{50}	14 nM	Inhibition of KRAS G12C mutant in human NCI-H358 cells assessed as reduction in ERK phosphorylation

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				incubated for 3 hrs by in-cell western method
	NCI-H358	IC_{50}	6 nM	Antiproliferative activity against human NCI-H358 cells assessed as reduction in cell viability measured after 3 days by Celltiter-Glo assay
	NCI-H358	IC_{50}	9.2 nM	Antiproliferative activity against human NCI-H358 cells harboring KRAS p.G12C mutant assessed as inhibition of cell growth incubated for 72 hrs by cell count reagent SF based assay
	PaTu 8988t	IC_{50}	3 μM	Antiproliferative activity against human PaTu 8988t cells assessed as reduction in cell viability measured after 3 days by Celltiter-Glo assay

In Vitro

MRTX849 (0.1-10000 nM; 3 天 /2D 条件，12 天 /3D 条件) 对绝大多数 KRAS G12C 突变体细胞系的生长有明显的抑制作用，其 IC50 在 2D 条件下为 10~973 nM，3D 条件为 0.2~1042 nM[1]。

MRTX849 (0.24-1000nM; 24 小时) 抑制 KRAS 依赖的信号转导靶点，包括 ERK1/2 磷酸化 (Thr202/Tyr204 ERK1; pERK)、S6 磷酸化.

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；口腔灌胃.；每日一次至第 16 天) 在耐受良好的剂量范围内显示剂量依赖性抗肿瘤疗效，MRTX849 的最大有效剂量在 30-100 mg/kg/天之间[1]。

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.

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Solvent&Solubility

细胞实验:

DMSO 中的溶解度 : 25 mg/mL (41.38 mM; 超声助溶 (<60°C); 吸湿的 DMSO 对产品的溶解度有显著影响，请使用新开封的 DMSO)

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

动物实验：

请根据您的 实验动物和给药方式 选择适当的溶解方案。

以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用；

以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

方案 一

请依序添加每种溶剂： 5% DMSO → 40% PEG300 → 5% Tween-80 → 50% Saline

Solubility: ≥ 2.62 mg/mL (4.34 mM); 澄清溶液

方案 二

请依序添加每种溶剂： 10% DMSO → 40% PEG300 → 5% Tween-80 → 45% Saline

Solubility: ≥ 2.5 mg/mL (4.14 mM); 澄清溶液

此方案可获得 ≥ 2.5 mg/mL（饱和度未知）的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；再向上述体系中加入 50 μL Tween-80，混合均匀；然后再继续加入 450 μL 生理盐水 定容至 1 mL。

生理盐水的配制：将 0.9 g 氯化钠，溶解于 ddH_2O 并定容至 100 mL，可以得到澄清透明的生理盐水溶液。

方案 三

请依序添加每种溶剂： 10% DMSO → 90% Corn Oil

Solubility: ≥ 2.5 mg/mL (4.14 mM); 澄清溶液

此方案可获得 ≥ 2.5 mg/mL（饱和度未知）的澄清溶液，此方案实验周期在半个月以上的动物实验酌情使用。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。

参考文献

[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.

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[3]. 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.
[4]. Awad MM, Liu S, Rybkin II, et al. Acquired Resistance to KRASG12C Inhibition in Cancer. N Engl J Med. 2021;384(25):2382-2393.

完整储备液配制表：

请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

可选溶剂	质量 / 溶剂体积 / 浓度	1 mg	5 mg	10 mg	25 mg
DMSO	**1 mM**	1.6553 mL	8.2765 mL	16.5530 mL	41.3825 mL
	5 mM	0.3311 mL	1.6553 mL	3.3106 mL	8.2765 mL
	10 mM	0.1655 mL	0.8277 mL	1.6553 mL	4.1383 mL
	15 mM	0.1104 mL	0.5518 mL	1.1035 mL	2.7588 mL
	20 mM	0.0828 mL	0.4138 mL	0.8277 mL	2.0691 mL
	25 mM	0.0662 mL	0.3311 mL	0.6621 mL	1.6553 mL
	30 mM	0.0552 mL	0.2759 mL	0.5518 mL	1.3794 mL
	40 mM	0.0414 mL	0.2069 mL	0.4138 mL	1.0346 mL