产品名称：**ARS-853**
产品别名：**ARS-853**

生物活性：

Description	ARS-853 is a cell-active, selective, covalent KRAS G12C inhibitor with an IC50 of 2.5 μM. ARS-853 inhibits mutant KRAS-driven signaling by binding to the GDP-bound oncoprotein and preventing activation[1][2].
IC_{50} & Target	KRAS(G12C)
	2.5 μM (IC_{50})
In Vitro	ARS853 is designed to bind $KRAS^{G12C}$ with high affinity. Treatment of $KRAS^{G12C}$-mutant lung cancer cells with ARS853 reduces the level of GTP-bound KRAS by more than 95% (10 μM). ARS853 inhibits proliferation with an inhibitory concentration 50% (IC_{50}) of 2.5 μM, which is similar to its IC_{50} for target inhibition. ARS853 (10 μM) inhibits effector signaling and cell proliferation to varying degrees in six $KRAS^{G12C}$ mutant lung cancer cell lines, but not in non-$KRAS^{G12C}$ models. Similarly, it completely suppresses the effects of exogenous $KRAS^{G12C}$expression on KRAS-GTP levels, KRAS-BRAF interaction, and ERK signaling. ARS-853 treatment also induces apoptosis in four $KRAS^{G12C}$ mutant cell lines. ARS853 selectively reduces KRAS-GTP levels and RAS-effector signaling in $KRAS^{G12C}$-mutant cells, while inhibiting their proliferation and inducing cell death[1]. ARS-853 inhibits mutant KRAS-driven signaling by binding to the GDP-bound oncoprotein and preventing activation[2].
Solvent&Solubility	***In Vitro:***
	DMSO : 33.33 mg/mL (**76.99 mM**; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3098 mL	11.5489 mL	23.0979 mL
	5 mM	0.4620 mL	2.3098 mL	4.6196 mL
	10 mM	0.2310 mL	1.1549 mL	2.3098 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。

In Vivo:

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

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

Solubility: ≥ 2.5 mg/mL (5.77 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.77 mM，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；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)

Solubility: ≥ 2.5 mg/mL (5.77 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.77 mM，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 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.77 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.77 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 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。
References	[1]. Lito P, et al. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. Science. 2016 Feb 5;351(6273):604-8. [2]. Patricelli MP, et al. Selective Inhibition of Oncogenic KRAS Output with Small Molecules Targeting the Inactive State. Cancer Discov. 2016 Mar;6(3):316-29.
实验参考：	
Kinase Assay	Purified KRAS (1 μM) is incubated EDTA (10 mM) and GDP (1 mM) or GTPγS (1 mM) at room temperature for 1 h followed by addition of $MgCl_2$ (1 mM) to terminate the reaction. ARS853 (1 μM) is then added and the mixture is incubated for another hour at room temperature. HEK293 cells expressing various KRAS mutants are treated with ARS853. Proteins are extracted using a buffer containing 9M urea, 10 mM DTT and 50 mM ammonium bicarbonate, pH 8, heated to 65°C for 15 min and alkylated using 50 mM iodoacetamide at 37°C for 30 min. The samples are desalted by gel filtration in Zeba spin desalting plates followed by addition of sequencing-grade trypsin to a concentration of 10 μg/ml, and incubation for one hour at 37°C. Heavy isotopic standards (25 fmol) of the $KRAS^{G12C}$ target peptide and KRAS normalization peptide are added to the samples followed by desalting in Strata-X polymeric reverse phase plates. LC-MS/MS analysis is performed in a Q Exactive quadrupole orbitrap mass spectrometer under standard condition. The amount of $KRAS^{G12C}$ bound by the drug is determined by the ratio of the modified G12C peptide to that of the heavy isotopic standards[1].
References	[1]. Lito P, et al. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. Science. 2016 Feb 5;351(6273):604-8. [2]. Patricelli MP, et al. Selective Inhibition of Oncogenic KRAS Output with Small Molecules Targeting the Inactive State. Cancer Discov. 2016 Mar;6(3):316-29.