ARS-853

Cat. No.: HY-19706

CAS No.: 1629268-00-3

Molecular Formula: $C_{22}H_{29}ClN_4O_3$

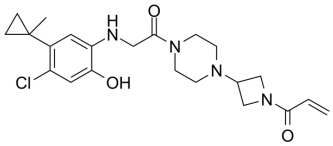
Molecular Weight: 432.94

Target: Ras; Apoptosis

Pathway: GPCR/G Protein; MAPK/ERK Pathway; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (57.74 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / 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

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 (5.77 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.77 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.77 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (4.62 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

ARS-853 is a cell-active, selective, covalent KRAS G12C inhibitor with an IC_{50} 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Discov. 2020 Dec;10(12):1950-1967.
- THE DEPARTMENT OF CANCER BIOLOGY.2020. 28103931.

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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.

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