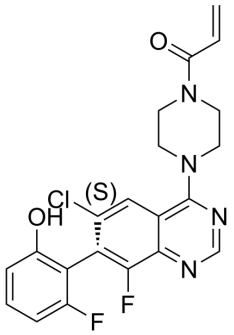
ARS-1620

Cat. No.:	HY-U00418
CAS No.:	1698055-85-4
Molecular Formula:	$C_{21}H_{17}ClF_2N_4O_2$
Molecular Weight:	430.84
Target:	Ras
Pathway:	GPCR/G Protein; MAPK/ERK Pathway
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 : 125 mg/mL (290.13 mM; Need ultrasonic)
H_2O : 11 mg/mL (25.53 mM; ultrasonic and adjust pH to 3 with HCl)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3210 mL	11.6052 mL	23.2105 mL
	5 mM	0.4642 mL	2.3210 mL	4.6421 mL
	10 mM	0.2321 mL	1.1605 mL	2.3210 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: ≥ 2.08 mg/mL (4.83 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.83 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.83 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

ARS-1620 is an atropisomeric selective $KRAS^{G12C}$ inhibitor with desirable pharmacokinetics.

IC_{50} & Target

KRAS(G12C)

In Vitro

ARS-1620 is an atropisomeric selective $KRAS^{G12C}$ inhibitor with desirable pharmacokinetics. ARS-1620 exhibits complete growth suppression of p.G12C cell lines (IC_{50}=150 nM) with relatively benign effects on control cell lines. It is found that ARS-

	1620 significantly reduces expression of the gene set in p.G12C mutant cells in a time-dependent manner but not in the p.G12S mutant cells. Following a 5-day treatment period, only a minority of G12C mutant cell lines are sensitive to ARS-1620 under monolayer culture conditions, whereas in 3D-spheroid conditions, ARS-1620 elicits a robust response (p=0.0140)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Following a single oral dose or 5 consecutive daily doses, ARS-1620 yields average peak tumor concentrations of 1.5 μM (50 mg/kg) and 5.5 μM (200 mg/kg), respectively, that enables significant $KRAS^{G12C}$ target occupancy (>=70% G12C-TE at 200 mg/kg) for >24 hr. In MIAPaCa2 xenografts (p.G12C), ARS-1620 significantly inhibits tumor growth (p<0.001) in a dose-dependent manner with marked regression at a dose of 200 mg/kg, given once daily. Across all tumor models employed, ARS-1620 is well tolerated over the entire 3-week treatment period. Moreover, there are no observed clinical signs or toxicity of ARS-1620 in CD-1 mice even at oral doses up to 1,000 mg/kg administered daily over a 7-day period. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	5×10^4 cells are seeded into 24 well ULA-plates and allowed to rest overnight. Cells are then treated with DMSO or ARS-1620. After 2 days of treatment, apoptosis and cell death is measured by staining with annexinV-APC and prodidium iodide or by 70% ethanol fixation followed by FxCycle Violet staining to measure DNA content (cell cycle) and percentage of sub-diploid events by flow cytometry[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	For pharmacokinetic (PK) studies 6- to 8-week-old male BALB/c mice are used. To determine oral bioavailability, mice are treated with ARS-1620 by a single intravenous (IV) bolus or oral gavage administration at the doses of 2 and 10 mg/kg, respectively. ARS-1620 concentration in plasma is quantified by LC-MS/MS-based methods. Pharmacokinetic parameters are estimated from mean plasma concentration-time profiles. The area under the curve (AUC) is calculated from time versus concentration data using the linear trapezoidal rule. The oral bioavailability is calculated as the ratio of AUC for ARS-1620 from oral and IV dosage. The calculation is normalized by relative doses[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Med. 2019 Apr;25(4):628-640.
- Clin Cancer Res. 2021 May 1;27(9):2533-2548.
- Clin Cancer Res. 2020 Nov 15;26(22):5962-5973.
- Clin Cancer Res. 2020 Apr 1;26(7):1633-1643.
- Cell Death Discov. 2023 Feb 6;9(1):45.

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REFERENCES

[1]. Janes MR, et al. Targeting KRAS Mutant Cancers with a Covalent G12C-Specific Inhibitor. Cell. 2018 Jan 25;172(3):578-589.e17.

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

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