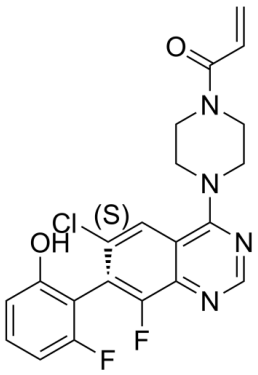
Data Sheet

Product Name:	ARS-1620
Cat. No.:	CS-0035119
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
Solubility:	H2O : 11 mg/mL (25.53 mM; ultrasonic and adjust pH to 3 with HCl); DMSO : 125 mg/mL (290.13 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

ARS-1620 is an atropisomeric selective **KRAS^{G12C}** inhibitor with desirable pharmacokinetics. IC50 & Target: KRAS^{G12C}[1] ***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]. ***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.

PROTOCOL (Extracted from published papers and Only for reference)

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]. **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].

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.

CAIndexNames:

2-Propen-1-one, 1-[4-[(7S)-6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)-4-quinazolinyl]-1-piperazinyl]-

SMILES:

C=CC(N1CCN(C2=C3C=C(Cl)[C@]([C@]4=C(O)C=CC=C4F)=C(F)C3=NC=N2)CC1)=O.[S]

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