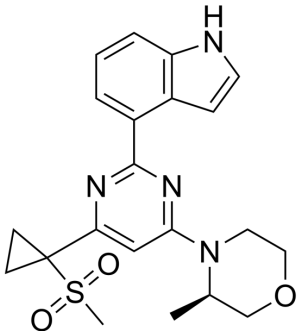
AZ20

Cat. No.:	HY-15557
CAS No.:	1233339-22-4
Molecular Formula:	$C_{21}H_{24}N_4O_3S$
Molecular Weight:	412.51
Target:	ATM/ATR
Pathway:	Cell Cycle/DNA Damage; PI3K/Akt/mTOR
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 : ≥ 100 mg/mL (242.42 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4242 mL	12.1209 mL	24.2418 mL
5 mM	0.4848 mL	2.4242 mL	4.8484 mL
10 mM	0.2424 mL	1.2121 mL	2.4242 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 (6.06 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.06 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZ20 is a potent and selective inhibitor of ATR with an IC_{50} of 5 nM, and has 8-fold selectivity against mTOR (IC_{50}=38 nM).

IC_{50} & Target

ATR	mTOR	PI3Kα
5 nM (IC_{50})	38 nM (IC_{50})	13000 nM (IC_{50})

In Vitro

AZ20 inhibits ATR immunoprecipitated from HeLa nuclear extracts with an IC_{50} of 5 nM and ATR mediated phosphorylation of Chk1 in HT29 colorectal adenocarcinoma tumor cells with an IC_{50} of 50 nM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	AZ20 (25, 50 mg/kg, p.o.) has high permeability combined with good stability to rat hepatocytes and, despite the lack of progress in achieving markedly higher solubility, has respectable bioavailability in a low dose rat PK study. AZ20 (25, 50 mg/kg, p.o.) leads to significant tumor growth inhibition in female nude mice bearing LoVo tumors[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Compound dose ranges are created by diluting in 100% DMSO and then further into assay medium (EMEM, 10% FCS, 1% glutamine) using a Labcyte Echo acoustic dispensing instrument. Cells are plated in 384-well Costar plates at 9×10^4 cells per mL in 40 µL of EMEM, 10% FCS, 1% glutamine and grown for 24 h. Following addition of compound the cells are incubated for 60 min. A final concentration of 3 µM 4NQO (prepared in 100% DMSO) is then added using the Labcyte Echo, and the cells are incubated for a further 60 min. The cells are fixed by adding 40 µL of 3.7% v/v formaldehyde solution for 20 min. After removal of fix, cells are washed with PBS and permeabilized in 40 µL of PBS containing 0.1% Triton X-100. The cells are then washed, and 15 µL primary antibody solution (pChk1 Ser345) is added. The plates are incubated at 4°C overnight. The primary antibody is then washed off, and 20 µL of secondary antibody solution and 1 µM Hoechst 33258 added for 90 min at room temperature. The plates are washed and left in 40 µL of PBS. Plates are then read on an ArrayScan VTI instrument to determine staining intensities, and dose responses are obtained and used to determine the IC_{50} values for the compounds. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Female Swiss nu/nu mice are housed in negative pressure isolators. LoVo tumor xenografts are established in 8- to 12-week-old mice by injecting 1×10^7 tumor cells subcutaneously (100 µL in serum free medium) on the left dorsal flank. Animals are randomized into treatment groups when tumors become palpable. AZ20 is prepared in 10% DMSO/40% propylene glycol/50% water and administered orally. Tumors are measured up to three times per week with calipers. Tumor volumes are calculated and the data plotted using the geometric mean for each group versus time. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2022 Nov 28;13(1):7212.
- Nat Commun. 2019 Jul 2;10(1):2910.
- Mol Cell. 2021 Mar 4;81(5):1084-1099.e6.
- Cell Syst. 2020 Jan 22;10(1):66-81.e11.
- Cell Syst. 2020 Jan 22;10(1):66-81.e11.

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REFERENCES

[1]. Foote KM, et al. Discovery of 4-{4-[(3R)-3-Methylmorpholin-4-yl]-6-[1-(methylsulfonyl)cyclopropyl]pyrimidin-2-yl}-1H-indole (AZ20): a potent and selective inhibitor of ATR protein kinase with monotherapy in vivo antitumor activity. J Med Chem. 2013 Mar 14

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