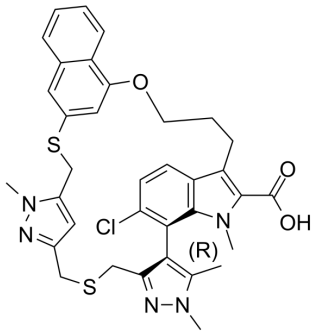
AZD-5991

Cat. No.:	HY-101533
CAS No.:	2143061-81-6
Molecular Formula:	$C_{35}H_{34}ClN_5O_3S_2$
Molecular Weight:	672.26
Target:	Bcl-2 Family
Pathway:	Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (371.88 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4875 mL	7.4376 mL	14.8752 mL
	5 mM	0.2975 mL	1.4875 mL	2.9750 mL
	10 mM	0.1488 mL	0.7438 mL	1.4875 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 (3.09 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (3.09 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (3.09 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (3.09 mM); Suspended solution; Need ultrasonic
5. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.09 mM); Clear solution
6. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.09 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZD-5991 is a potent and selective Mcl-1 inhibitor with an IC_{50} of 0.7 nM in FRET assay and a K_d of 0.17 nM in surface plasmon

	resonance (SPR) assay[1].	
IC_{50} & Target	Mcl-1 0.7 nM (IC_{50})	Mcl-1 0.17 nM (Kd)
In Vitro	The selectivity of AZD-5991 is evaluated against pro-survival Bcl-2 family members using FRET assays. AZD-5991 is selective for Mcl-1 (IC_{50} 0.72 nM, K_i=200 pM) vs. Bcl-2 (IC_{50}=20 μM, K_i=6.8 μM), Bcl-xL (IC_{50}=36 μM, K_i=18 μM), Bcl-w (IC_{50}=49 μM, K_i=25 μM), and Bfl-1 (IC_{50}=24 μM, K_i=12 μM). MOLP-8, MV4-11, and NCI-H23 cells are treated with AZD5991 (EC_{50}=0.033, 0.024, 0.19 μM, respectively).AZD5991 binds directly to Mcl-1 and induces rapid apoptosis in cancer cells, most notably myeloma and acute myeloid leukemia, by activating the Bak-dependent mitochondrial apoptotic pathway. AZD5991 reduces the levels of Mcl-1 protein in AZD5991-sensitive but not in AZD5991-resistant MM cell lines further supporting the notion that activation of caspases by AZD5991 reduces Mcl-1 protein levels in AZD5991-sensitive cell lines[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	A single intravenous (i.v.) dose of AZD5991 leads to a dose-dependent antitumor effect ranging from tumor growth inhibition (TGI) to tumor regression (TR). Ten days after treatment, AZD5991 shows 52% and 93% TGI ($p<0.0001$) at 10 and 30 mg/kg, respectively. At the same time point, AZD5991 at 60 mg/kg leads to 99% TR with no detectable tumors in 6 out of 7 mice, while complete TR is seen in 7 out of 7 mice in the 100 mg/kg dose group. AZD5991 also shows a dose-dependent duration of response with tumors in the 100 mg/kg group growing back later than those in the 60 mg/kg group. The magnitude of in vivo tumor efficacy is correlated with activation of caspase-3 in the tumor and concentration of AZD5991 in plasma. Treatment with AZD5991 was well tolerated at all dose levels with no significant body weight loss. A single dose of AZD5991 36 days after the first dose causes tumor regression in 4 out of 4 mice. In mice dosed with AZD5991 at 100 mg/kg on day 0 and day 1, tumors grow back later than those dosed with a single dose of AZD5991 at the same dose level[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Animal Administration [1]	Mice and Rats[1] In mice, drugs (e.g., AZD5991; 10-100 mg/kg) are dosed intravenously in a volume of 5 mL/kg except for Venetoclax that is dosed orally in a volume of 10 mL/kg. One million MV4-11, five million MOLP-8, ten million NCI-H929 or five million OCI-AML3 cells are injected subcutaneously in the right flank of mice in a volume of 0.1 mL. In rats, AZD5991 (10-100 mg/kg) is dosed intravenously in a volume of 10 mL/kg. Ten million MV4-11 cells are injected subcutaneously in the right flank of rats in a volume of 0.1 mL. Tumor volumes (measured by caliper), animal body weight, and tumor condition are recorded twice weekly for the duration of the study. The tumor volume is calculated[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Dis. 2022 Apr 28;13(4):410.
- Cell Death Dis. 2021 Jul 27;12(8):741.
- Apoptosis. 2022 Aug 9.
- Int J Cancer. 2020 Oct 15;147(8):2176-2189.
- Cells. 2022 Sep 3;11(17):2752.

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REFERENCES

[1]. Tron AE, et al. Discovery of Mcl-1-specific inhibitor AZD5991 and preclinical activity in multiple myeloma and acute myeloid leukemia. Nat Commun. 2018 Dec 17;9(1):5341.

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