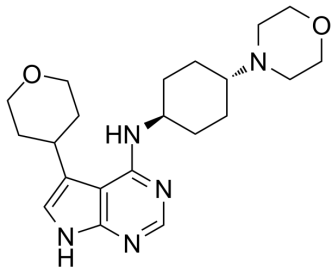
AZ1495

Cat. No.:	HY-111101
CAS No.:	2196204-23-4
Molecular Formula:	$C_{21}H_{31}N_5O_2$
Molecular Weight:	385.5
Target:	IRAK
Pathway:	Immunology/Inflammation
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 10 mg/mL (25.94 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5940 mL	12.9702 mL	25.9403 mL
	5 mM	0.5188 mL	2.5940 mL	5.1881 mL
	10 mM	0.2594 mL	1.2970 mL	2.5940 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: ≥ 1 mg/mL (2.59 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (2.59 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1 mg/mL (2.59 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZ1495, a weak base, is a potent orally active interleukin-1 receptor associated kinase 4 (IRAK4) inhibitor. AZ1495 has a favorable physicochemical and kinase selectivity for IRAK4 and IRAK1 with IC_{50} values of 0.005 μM and 0.023 μM, respectively. AZ1495 has IRAK4 inhibition with a K_d value of 0.0007 μM. AZ1495 can be used for the research of diffuse large B-cell lymphoma (DLBCL)[1].

IC_{50} & Target				
	IRAK4	IRAK1	CLK1	CLK2
	5 nM (IC_{50})	23 nM (IC_{50})	50 nM (IC_{50})	5 nM (IC_{50})

	CLK4 8 nM (IC_{50})	haspin 4 nM (IC_{50})

In Vitro

AZ1495 (compound 28) (10 μM,1 h) has kinase selectivity for IRAK4 with IC_{50} values of 0.005 μM (enzyme assay) and 0.052 μM (cellular assay), respectively[1].
AZ1495 (10 μM,1 h) has kinase inhibition for IRAK4 with an IC_{50} value of 0.005 μM and K_d value of 0.0007 μM[1].
AZ1495 (0.001-100 μM, 72 h) inhibits NF-κB activation and growth of ABC-DLBCL cell lines in a dosedependent manner[1].
AZ1495 (0-3.3 μM, 14 h) completely inhibits NF-κB signaling and induces cell death at lower concentration in combination with a BTK inhibitor in OCI-LY10 cells[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	OCI-LY10 and SUDHL2 cells
Concentration:	0.001-100 μM
Incubation Time:	72 h
Result:	Inhibited growth of OCI-LY10 cells in a dosedependent manner, whereas SUDHL2, a GCB-cell line was not sensitive and no increased cell killing to IRAK4 inhibitor. Increased the cell death in OCI-LY10 cells upon increasing concentrations of compound 28 and BTK ibrutinib.

Western Blot Analysis[1]

Cell Line:	OCI-LY10 cells
Concentration:	0-3.3 μM
Incubation Time:	14 h
Result:	Inhibited IκBα phosphorylation with dose-dependentence in OCI-LY10 cells. Showed induction of apoptosis combination with 10 nM ibrutinib by cleavage of caspase 3 in OCI-LY10 cells.

In Vivo

AZ1495 (compound 28) (oral, daily, 12.5 mg/kg) leds to tumor regression combination with ibrutinib in an ABC-DLBCL mouse model (OCI-LY10 cells)[1].
AZ1495 (iv., 2 mg/kg and oral, 5mg/kg) is characterized by high clearance (Cl) in rat (75 mL/min/kg) and moderate predictions based on hepatocyte data (Clint 15 μl/min/106 cells, predicted clearance 42 mL/min/kg) with low bioavailability consistent with a high first pass effect[1].
AZ1495 (iv., 1 mg/kg) has low the amount of active renal secretion occurring in the dog[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	CB.17 SCID mice[1]
Dosage:	12.5 mg/kg
Administration:	oral, daily, 12.5 mg/kg
Result:	Had modest anti-tumor activity as single agents but a combination ofibrutinib led to tumor regression and is well tolerated.

Animal Model:	rat[1]

Dosage:	2 mg/kg, 5mg/kg
Administration:	iv., 2 mg/kg and oral, 5mg/kg
Result:	

Species	Dose (mg/kg)	Cl (mL/min/kg)	Vss(L/kg)	PO halflife (h)	IV halflife (h)	Fabs (%)	F (%)
Rat	2、5	75	2.1	2.0	0.8	100	28
Dog	1	29	3.0	-	3.3	-	-

Animal Model:	dog[1]
Dosage:	1 mg/kg
Administration:	iv., 1 mg/kg
Result:	

Species	Dose (mg/kg)	Cl (mL/min/kg)	Vss(L/kg)	PO halflife (h)	IV halflife (h)	Fabs (%)	F (%)
Rat	2、5	75	2.1	2.0	0.8	100	28
Dog	1	29	3.0	-	3.3	-	-

REFERENCES

[1]. Scott JS, et al. Discovery and Optimization of Pyrrolopyrimidine Inhibitors of Interleukin-1 Receptor Associated Kinase 4 (IRAK4) for the Treatment of Mutant MYD88L265P Diffuse Large B-Cell Lymphoma. J Med Chem. 2017 Dec 28;60(24):10071-10091.

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