AZD1080

Cat. No.: HY-13862

CAS No.: 612487-72-6

Molecular Formula: $C_{19}H_{18}N_4O_2$

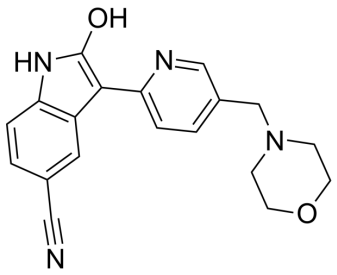
Molecular Weight: 334.37

Target: GSK-3

Pathway: PI3K/Akt/mTOR; Stem Cell/Wnt

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 : 21.35 mg/mL (63.85 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.9907 mL	14.9535 mL	29.9070 mL
	5 mM	0.5981 mL	2.9907 mL	5.9814 mL
	10 mM	0.2991 mL	1.4953 mL	2.9907 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 (7.48 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.48 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZD1080 is a potent and selective GSK3 inhibitor. AZD1080 inhibits recombinant human GSK3α and GSK3β with pK_i (IC_{50}) of 8.2 (6.9 nM) and 7.5 (31 nM), respectively.

IC_{50} & Target

GSK-3α 8.2 (pKi)	GSK-3β 7.5 (pKi)	cdk5 6.4 (pKi)	cdk2 5.9 (pKi)
cdk1 5.7 (pKi)			

In Vitro

AZD1080 shows selectivity against cdk2 (pK_i=5.9; 1150 nM; 37-fold), cdk5 (pK_i=6.4; 429 nM; 14-fold), cdk1 (pK_i=5.7; 1980 nM;

	64-fold) and Erk2 (pK_i< 5; >10 μM; >323-fold). AZD1080 (at 10 μM) is also evaluated for pan-kinase selectivity and showed good overall selectivity versus 23 kinases, as well as against 65 different receptors, enzymes and ion channels in MDS Pharma screen (< 50% effect at 10 μM AZD1080). Concentration-dependent inhibition of tau phosphorylation is observed for AZD1080 (IC_{50}=324 nM) and the non-selective reference GSK3 inhibitor LiCl (IC_{50}=1.5 mM) indicating that AZD1080 is several orders of magnitude more potent than LiCl[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The pharmacokinetic analysis in blood after oral administration revealed that AZD1080 has a good oral bioavailability in rats (15-24%) with a half-life of 7.1 h, making AZD1080 attractive for further in vivo testing. The subchronic (3 days) oral treatment with AZD1080 at 4 or 15 μmol/kg significantly blocked the MK-801-induced memory deficit (AZD1080 vs. MK-801, $p<0.05$ at 4 μmol/kg and $p<0.01$ at 15 μmol/kg) in mice, raising the hypothesis that longer treatment may be required to prime the synapses to function effectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The GSK3β, Cdk2, and Cdk5 K_i's are determined using scintillation proximity assays and kinetic analyses. The GSK3α assay is performed for the GSK3β assay. The K_M value of ATP used to calculate the K_i value for GSKα is 10 μM. Inhibition of Cdk1 is performed. The K_M value of ATP used to calculate the K_i value is 51 μM. Erk2 activity is determined using an Ser/Thr kinase SPA kit, p42 MAPK kinase (20 U/well), and biotinylated MBP. The K_M value of ATP used to calculate the K_i value is 71 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] A total of 161 male C57BL/6 mice, 8-12 weeks of age, are used. The animals are kept in conventional housing (3-5 mice per cage) and fed standard rodent chew and tap water ad libitum. Typically 9-12 mice are included in each experimental group and 2-4 mice in the satellite groups (for determination of compound exposure in plasma and brain, see below). AZD1080 (4.0 or 15 μmol/kg) or vehicle (water with 0.5% ascorbic acid, 0.01% EDTA, pH 2.0) is administered by oral gavage (10 mL/kg) acutely or subchronically (twice daily) for 3 days. The training trial is performed at 1.5, 3, or 5 h after final administration with AZD1080. To disrupt learning, the mice received subcutaneous administration of MK-801 (0.1 or 0.15 mg/kg; (+)-MK.801 hydrogen maleate) or vehicle (saline) 30 min before the training trial. Rats[1] A total of 71 adult male Sprague-Dawley rats (250-300 g) are used. The rats receive an acute dose of AZD1080 (1, 3 or 10 μ mol/kg) or vehicle (water with 0.5% ascorbic acid, 0.01% EDTA, pH 2.0) via oral gavage (dosing volume 5 mL/kg). At 1, 2, 3, 6, or 24 h after administration the rats are anesthetized and blood, from abdominal aorta, is sampled in heparin micro tainer tubes. Peripheral blood mononuclear cells (PBMC) are isolated from the blood samples. Separate blood samples are obtained for plasma processing and subsequent bioanalysis. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Br J Cancer. 2023 Jan 30.
- Biochem Biophys Res Commun. 2022 May 21;605:171-176.
- University of Rijeka. Derartment of biotechnology
- Patent. US20170165230A1.

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REFERENCES

[1]. Georgievska B, et al. AZD1080, a novel GSK3 inhibitor, rescues synaptic plasticity deficits in rodent brain and exhibits peripheral target engagement in humans. J Neurochem. 2013 May;125(3):446-56.

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