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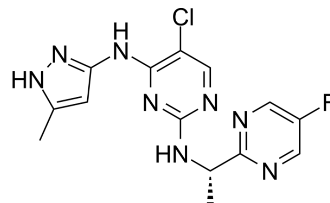
Product Data Sheet

AZD-1480

Cat. No.:	HY-10193
CAS No.:	935666-88-9
Molecular Formula:	$C_{14}H_{14}ClFN_8$
Molecular Weight:	348.77
Target:	JAK
Pathway:	Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt
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 : 50 mg/mL (143.36 mM; Need ultrasonic)

Preparing Stock Solutions

Concentration \ Solvent / Mass	1 mg	5 mg	10 mg
1 mM	2.8672 mL	14.3361 mL	28.6722 mL
5 mM	0.5734 mL	2.8672 mL	5.7344 mL
10 mM	0.2867 mL	1.4336 mL	2.8672 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 (7.17 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.17 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.17 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZD-1480 is an ATP-competitive inhibitor of JAK1 and JAK2 with IC_{50}s of 1.3 nM and <0.4 nM, respectively[1].

IC_{50} & Target

JAK2	JAK1
<0.4 nM (IC_{50})	1.3 nM (IC_{50})

In Vitro

AZD-1480 (5μM) induces G2/M arrest and cell death by inhibiting Aurora kinases[1].
AZD-1480 is a potent JAK2 inhibitor that can suppress growth, survival, as well as FGFR3 and STAT3 signaling and

downstream targets including Cyclin D2 in human multiple myeloma cells. At low micromolar concentrations, AZD-1480 blocks cell proliferation and induces apoptosis of myeloma cell lines[2].
AZD-1480 effectively blocks constitutive and stimulus-induced JAK1, JAK2, and STAT-3 phosphorylation in both human and murine glioma cells, and leads to a decrease in cell proliferation and induction of apoptosis[3].
AZD-1480 is a potent, competitive small-molecule inhibitor of JAK1/2 kinase, and that it is capable of inhibiting STAT3 phosphorylation and tumor growth in a STAT3-dependent manner. AZD-1480 inhibits tumor angiogenesis and metastasis in part by affecting the tumor microenvironment[4].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

AZD-1480 inhibits the STAT3 phosphorylation in an xenograft model of human solid tumors and multiple myeloma[1].
In vivo, AZD-1480 inhibits the growth of subcutaneous tumors and increases survival of mice bearing intracranial glioblastoma (GBM) tumors by inhibiting STAT-3 activity, indicating that pharmacologic inhibition of the JAK/STAT-3 pathway by AZD-1480 should be considered for study in the treatment of patients with GBM tumors[3].
AZD-1480 blocks lung infiltration of myeloid cells and formation of pulmonary metastases in both mouse syngeneic experimental and spontaneous metastatic models. Furthermore, AZD-1480 reduces angiogenesis and metastasis in a human xenograft tumor model[4].
AZD-1480 suppresses the growth of human solid tumor xenografts harboring persistent Stat3 activity[5].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [5]

Inhibition studies of AZD1480 are performed using recombinant Jak1, Jak2, or Jak3 under buffer conditions of 50 mM HEPES pH 7.3, 1 mM DTT, 0.01% Tween-20, 50 mM/mL BSA, and 10 mM $MgCl_2$. Jak3 enzyme is expressed as N-terminal GST fusion in insect cells and purified by glutathione-affinity and size-exclusion chromatographies. Enzymes are assayed in the presence of AZD1480 (10 point dose response, in triplicate, from 8.3 μM to 0.3 nM in half-log dilution steps) using 1.5 μM peptide substrate (Jak1: FITC-C6-KKHTDDGYMPMSPGVA-NH2, Jak2 and Jak3: FAM-SRCtide) and screened under their respective ATP K_m (Jak1: 55 μM, Jak2: 15 μM, Jak3: 3 μM) and approximated physiological ATP concentration of 5 mM. Phosphorylated and unphosphorylated peptides are separated and quantified by a Caliper LC3000 system for calculating percent inhibition.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [4]

Renca or 786-O cells are suspended in DMEM medium with 5% FBS, and seeded in 96-well plates (5×10^3 per well) to allow adhesion and then treated with DMSO or AZD1480 for 48 hours. Cell viability is determined by MTS assay. Absorbance at 490 nm is measured with Mikrotek Laborsysteme. Mouse endothelial cells and splenic CD11b+/c- myeloid cells are enriched from tumor-bearing mice,and cultured in 5% FBS RPMI-1640 medium. HUVECs are cultured on collagen 1-coated plates in complete medium. All cells are treated with DMSO and AZD1480 at various doses for 24 hours. Cell viability is determined by counting cell number manually. All the experiments are repeated 3 times.
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Animal Administration [1]

For subcutaneous (s.c.) tumor model, 2.5×10^6 Renca or 786-O cells suspended in 100 μL PBS are injected into the flank of BALB/c or nude mice, respectively. When average tumor volume reaches approximately 100-150 mm^3, AZD1480 or vehicle is administered by oral gavage either once a day at the dose of 50 mg/kg, or twice daily at 30 mg/kg, as indicated. Tumor size is measured by caliper every other day. For experimental lung metastasis model, 0.1×10^6 Renca or 1×10^6 786-O cells suspended in 500 μL PBS are injected via tail vein to BALB/c or nude mice, respectively. Three days later, mice are orally treated with AZD1480 (50 mg/kg/d) or vehicle for 21 days for Renca tumors and 60 days for 786-O tumors respectively. For the Calu-6 model, 3×10^6 tumor cells in matrigel are implanted s.c. into the flanks of nude mice, randomized into vehicle (twice daily, BID) and drug treatment (AZD1480, 30 mg/kg BID) groups, and dosed orally daily for 19 days. For spontaneous lung metastasis model, 2×10^5 4T1 cells suspended in 100 μL PBS are injected in the mammary gland of female BALB/c mice by gently penetrating the skin. AZD1480 (50 mg/kg/d) or vehicle is given orally for 21 days.
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.
- Neuro Oncol. 2017 Jan;19(1):22-30.
- Clin Cancer Res. 2018 Apr 15;24(8):1917-1931.
- Leukemia. 2012 Oct;26(10):2233-44.
- Biomed Pharmacother. 2017 Nov;95:1799-1808.

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REFERENCES

[1]. Derenzini E, et al. The JAK inhibitor AZD1480 regulates proliferation and immunity in Hodgkin lymphoma. Blood Cancer J. 2011 Dec;1(12):e46.

[2]. Scuto A, et al. The novel JAK inhibitor AZD1480 blocks STAT3 and FGFR3 signaling, resulting in suppression of human myeloma cell growth and survival. Leukemia. 2011 Mar;25(3):538-50.

[3]. McFarland BC, et al. Therapeutic potential of AZD1480 for the treatment of human glioblastoma. Mol Cancer Ther. 2011 Dec;10(12):2384-93.

[4]. Xin H, et al. Antiangiogenic and antimetastatic activity of JAK inhibitor AZD1480. Cancer Res. 2011 Nov 1;71(21):6601-10.

[5]. Hedvat M, et al. The JAK2 inhibitor AZD1480 potently blocks Stat3 signaling and oncogenesis in solid tumors. Cancer Cell. 2009 Dec 8;16(6):487-9

[6]. Ni J, et al. Tyrosine receptor kinase B is a drug target in astrocytomas. Neuro Oncol. 2017 Jan;19(1):22-30.

Caution: Product has not been fully validated for medical applications. For research use only.

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