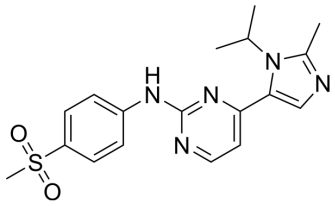
AZD-5438

Cat. No.:	HY-10012
CAS No.:	602306-29-6
Molecular Formula:	$C_{18}H_{21}N_5O_2S$
Molecular Weight:	371.46
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
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 : 100 mg/mL (269.21 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6921 mL	13.4604 mL	26.9208 mL
	5 mM	0.5384 mL	2.6921 mL	5.3842 mL
	10 mM	0.2692 mL	1.3460 mL	2.6921 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 (6.73 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.73 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.73 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZD-5438 is a potent CDK1, CDK2, and CDK9 inhibitor, with IC_{50}s of 16 nM, 6 nM, and 20 nM in cell-free assays, respectively. AZD-5438 shows less inhibition activity against GSK3β, CDK5 and CDK6[1].

IC_{50} & Target

cdk2-cyclin E 6 nM (IC_{50})	cdk2-cyclin A 45 nM (IC_{50})	cdk5-p25 14 nM (IC_{50})	cdk1-cyclin B1 16 nM (IC_{50})
cdk9-cyclin T 20 nM (IC_{50})	cdk6-cyclin D3 21 nM (IC_{50})	cdk4-cyclin D1 449 nM (IC_{50})	cdk7-cyclin H 821 nM (IC_{50})

In Vitro	AZD5438 potently inhibits the kinase activity of cyclin E-cdk2, cyclin A-cdk2, cyclin B1-cdk1, p25-cdk5, cyclin D3-cdk6, and cyclin T-cdk9 (IC_{50}, 6, 45, 16, 21, and 20 nM, respectively). AZD5438 potently inhibits the kinase activity of cyclin E-cdk2, cyclin A-cdk2, cyclin B1-cdk1, p25-cdk5, cyclin D3-cdk6, and cyclin T-cdk9 (IC_{50}, 6, 45, 16, 21, and 20 nM, respectively). In common with many other cdk inhibitors, AZD5438 also inhibits the kinase activity of p25-cdk5 and glycogen synthase kinase 3β in vitro (IC_{50}, 14 and 17 nM, respectively)[1]. AZD5438 significantly augments cellular radiosensitivity in NSCLC cells. Combined treatment with AZD5438 and irradiation also enhances tumor growth delay, with an enhancement factor ranging from 1.2-1.7[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AZD5438 (50 mg/kg twice daily or 75 mg/kg, p.o.) inhibits human tumor xenograft growth. In vivo, AZD5438 reduces the proportion of actively cycling cells. Further pharmacodynamic analysis of AZD5438-treated SW620 xenografts shows that efficacious doses of AZD5438 (>40% tumor growth inhibition) maintains suppression of biomarkers, such as phospho-pRbSer249/Thr252, for up to 16 hours following a single oral dose[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	AZD5438 is tested against solid tumor cell lines as previously described. Briefly, cells are incubated for 48 h with AZD5438 at a range of concentrations. At the end of incubation, the cells are pulsed with 5-bromo-2'-deoxyuridine (BrdUrd) and the amount of DNA synthesis is measured. The IC_{50} for inhibition of proliferation is specifically determined independently of cell death. Multiple myeloma cell lines are seeded into 96-well plates in RPMI 1640 supplemented with 10% FCS and glutamine and dosed with AZD5438 for 72 h. Cell growth is measured using AlamarBlue and GI_{50} values are calculated with reference to pretreatment control values. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	All human tumor xenografts except HX147 are established by s.c. injecting 100 µL of tumor cells (between 1×10^6 and 1×10^7 cells mixed 1:1 with Matrigel). HX147 tumors are derived from fragment implants (1 mm^3 pieces) from tumors taken from mice initially implanted s.c. with 1×10^7 cells. These tumor fragments are passaged in mice thrice before implant for antitumor work. Tumors are measured up to three times per week with calipers, tumor volumes are calculated, and the data are plotted as geometric mean for each group versus time, as previously described. Animals are randomized into treatment groups (typically n=10) when tumors reach a mean size of approximately >0.2 cm^3 and >0.5 cm^3 for mice and rats, respectively. AZD5438 is prepared in hydroxy-propyl-methyl-cellulose. Animals are given either AZD5438 (37.5-75 mg/kg) or vehicle control once or twice daily by oral gavage for appr 3 wk in each case. Tumor volume and percentage tumor growth inhibition (% TGI) are calculated as described previously. Statistical analysis of any change in tumor volume is carried out using a standard t test ($P<0.05$ is considered to be statistically significant). 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.
- Sci Adv. 2022 Jan 28;8(4):eabk2116.
- JACC Basic Transl Sci. 2023 Jul 19.
- Cell Chem Biol. 2018 Feb 15;25(2):135-142.e5.
- J Transl Med. 2022 Oct 2;20(1):444.

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REFERENCES

[1]. Byth KF, et al. AZD5438, a potent oral inhibitor of cyclin-dependent kinases 1, 2, and 9, leads to pharmacodynamic changes and potent antitumor effects in human tumor xenografts. Mol Cancer Ther. 2009 Jul;8(7):1856-66. Epub 2009 Jun 9.

[2]. Raghavan P, et al. AZD5438, an Inhibitor of Cdk1, 2, and 9, Enhances the Radiosensitivity of Non-Small Cell Lung Carcinoma Cells. Int J Radiat Oncol Biol Phys. 2012 Jul 12.

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