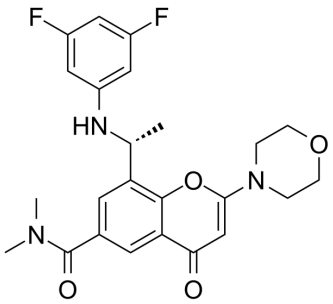
AZD8186

Cat. No.:	HY-12330
CAS No.:	1627494-13-6
Molecular Formula:	$C_{24}H_{25}F_2N_3O_4$
Molecular Weight:	457.47
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
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 : ≥ 35 mg/mL (76.51 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1859 mL	10.9297 mL	21.8594 mL
	5 mM	0.4372 mL	2.1859 mL	4.3719 mL
	10 mM	0.2186 mL	1.0930 mL	2.1859 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO/60% tri-ethylene glycol (TEG)/30% water
   Solubility: 15 mg/mL (32.79 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.75 mg/mL (6.01 mM); Clear solution
3. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.75 mg/mL (6.01 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.55 mM); Clear solution
5. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.55 mM); Clear solution
6. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.55 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	AZD8186 is a PI3K inhibitor, which potently inhibits PI3Kβ (IC_{50}=4 nM) and PI3Kδ ($IC50_{50}$=12 nM) with selectivity over PI3Kα (IC_{50}=35 nM) and PI3Kγ (IC_{50}=675 nM).

IC_{50} & Target	PI3Kβ	PI3Kδ	PI3Kα	PI3Kγ
	4 nM (IC_{50})	12 nM (IC_{50})	35 nM (IC_{50})	675 nM (IC_{50})

In Vitro

AZD8186 is a potent inhibitor of PI3Kβ with additional activity versus the PI3Kδ isoform. Tight-binding kinetics of AZD8186 means biochemical assays underestimate the absolute selectivity profile for PI3Ks. In a broad panel of protein and lipid kinase assays selectivity for PI3Kβ and δ is >100-fold versus 74 protein and lipid kinases. At 10 μM, AZD8186 had no significant binding to 442 other kinases in a KinomeScan screen. AZD8186 shows selectivity for PI3K family kinases, no other off-target activity is detected. In the PTEN-null line, MDA-MB-468 AZD8186 inhibits PI3Kβ-dependent activation of pAKT (Ser473) with an IC_{50} value of 3 nM. Potency in the PIK3CA-mutant line BT474c is 752 nM demonstrating selectivity for PI3Kβ over PI3Kα. IgM mediated stimulation of B cells results in phosphorylation of AKT through activation of PI3Kδ. AZD8186 inhibits IgM-stimulated phosphorylation of pAKT (Ser473) activation in JEKO cells with an IC_{50} value of 17 nM. In cell proliferation assays, AZD8186 inhibits proliferation of MDA-MB-468 cells with a GI_{50} value of 65 nM, IgM stimulated JEKO cell growth with an IC_{50} value of 228 nM. It only inhibited BT474c cell growth with an IC_{50} value of 1.981 μM consistent with its selectivity for PI3Kβ over PI3Kα[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

To assess single-agent efficacy of AZD8186 in vivo, antitumor activity is assessed in the PTEN-null TNBC models HCC70 and MDA-MB-468, and the prostate models PC3 and HID28. At 50 and 25 mg/kg twice a day, AZD8186 inhibits the growth of all four models. At 25 and 50 mg/kg, HCC70 is inhibited at 62% (P<0.001) and 85% (P<0.001), respectively, MDA-MB-468 is inhibited at 47% (P<0.001) and 76% (P<0.001), respectively, at end at of study, with regression early in the study. Efficacy in the PTEN-null prostate model, PC3 is less pronounced with 25 and 50 mg/kg giving maximal growth inhibition of 59% (P<0.001) and 64% (P<0.001), respectively. In contrast, AZD8186 gives 79% (P<0.001) growth inhibition in the PTEN-null prostate explant model HID28. In mouse, AZD8186 has a short half-life delivering a PK profile that results in intermittent cover over a 24 hours dosing interval. To increase the time of exposure, animals bearing PC3 tumors are co-dosed with AZD8186 in the presence of the Cyt P450 inhibitor ABT, which results in significantly increased exposure. This also increased the efficacy in the PC3 model with 86% (P<0.005) reduction in tumor growth achieved with 30 mg/kg AZD8186+ABT[1].

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PROTOCOL

Cell Assay [1]

Cells are exposed to AZD8186 at concentrations ranging from 3 to 0.01 μM for 2 hours. Cells are then lysed on ice with a buffer containing 25 mM Tris/HCL pH6.8, 3 mM EDTA, 3 mM EGTA, 50 mM NaF, 2 mM sodium orthovanadate, 270 mM sucrose, 10 mM β-glycerophosphate, 5 mM sodium pyrophosphate, and 0.5% Triton X-100 and protease and phosphatase inhibitors. Lysates are diluted with sample loading buffer, separated on 4% to 12% Bis-Tris Novex gels, transferred onto nitrocellulose membranes, and probed with primary antibodies overnight. After a washing step, membranes are incubated with HRP-tagged secondary antibodies and visualized[1].

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Animal Administration [1]

Mice[1]

The female CB17 SCID mice ages 6 to 8 weeks are used. HID28 in vivo experiments are performed under contract by Xentech, HID28 tumor fragments (approximately 40 mm^3) from donor animals are aseptically implanted subcutaneously in at the level of the interscapular region. Outbred athymic (nu/nu) male mice (HSD: Athymic Nude-Foxn1nu) weighing 18 to 25 g. For all animals studies groups are powered with a minimum of 8 animals per group. AZD8186 is generally formulated once weekly as a suspension in HPMC/Tween and dosed once or twice daily (0 and 6-8 hours). AZD8186 is formulated once weekly either alone in 10% DMSO/60% tri-ethylene glycol (TEG)/30% water for injection (WFI) or in the presence of ABT at 10 mg/mL. For twice daily dosing (0 and 6-8 hours), AZD8186 is co-dosed with ABT at 0 hours and administered alone as the single formulation at 6 to 8 hours. RP-56976 is formulated fresh in physiologic saline at 1.5 mg/mL and dosed as a single i.v. bolus dose at a rate of 0.1 mL/10 g on day 0, 24 hours before the administration of AZD8186.

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CUSTOMER VALIDATION

- Blood. 2019 Jan 3;133(1):70-80.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Diabetes. 2021 Oct 21;db210240.
- Oncotarget. 2020 Nov 3;11(44):3921-3932.
- bioRxiv. 2019 Oct.

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REFERENCES

[1]. Hancox U, et al. Inhibition of PI3Kβ signaling with AZD8186 inhibits growth of PTEN-deficient breast and prostate tumors alone and in combination with RP-56976. Mol Cancer Ther. 2015 Jan;14(1):48-58.

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