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Zuschläge

- Mindermengenzuschlag
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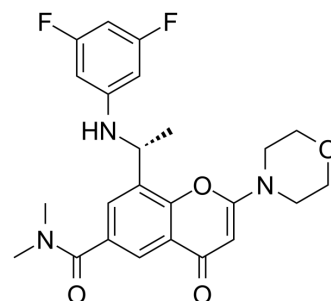
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AZD8186

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.

	Solvent Concentration	Mass	1 mg	5 mg	10 mg
Preparing Stock Solutions	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

- 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
- 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
- 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
- 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
- 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
- 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 PI3K β (IC ₅₀ =4 nM) and PI3K δ (IC ₅₀ =12 nM) with selectivity over PI3K α (IC ₅₀ =35 nM) and PI3K γ (IC ₅₀ =675 nM).			
IC₅₀ & Target	PI3K β 4 nM (IC ₅₀)	PI3K δ 12 nM (IC ₅₀)	PI3K α 35 nM (IC ₅₀)	PI3K γ 675 nM (IC ₅₀)
In Vitro	<p>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 IC₅₀ 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 IC₅₀ value of 17 nM. In cell proliferation assays, AZD8186 inhibits proliferation of MDA-MB-468 cells with a GI₅₀ value of 65 nM, IgM stimulated JEKO cell growth with an IC₅₀ value of 228 nM. It only inhibited BT474c cell growth with an IC₅₀ value of 1.981 μM consistent with its selectivity for PI3Kβ over PI3Kα^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>			
In Vivo	<p>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 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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>			

PROTOCOL

Cell Assay ^[1]	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[1]	<p>Mice^[1]</p> <p>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 mm³) 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.</p>

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

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 PI3K β 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.

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

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