

## Product Data Sheet

Product Name: AZD8186

Cat. No.: GC12576

### Chemical Properties

Cas. No. 1627494-13-6

Chemical Name (R)-8-(1-((3,5-difluorophenyl)amino)ethyl)-N,N-dimethyl-2-morpholino-4-oxo-4H-chromene-6-carboxamide

SMILES C[C@](NC1=CC(F)=CC(F)=C1)([H])C2=C3C(C(C=C(O3)N4CCOCC4)=O)=CC(C(N(C)C)=O)=C2

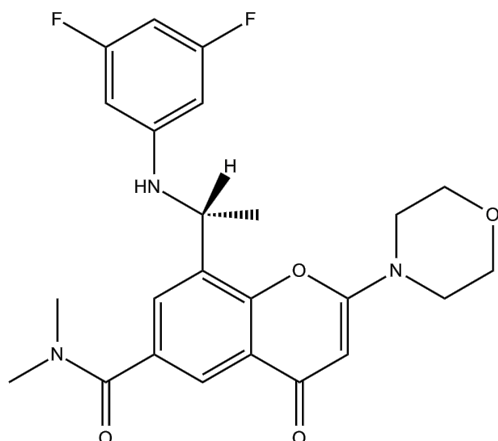
Formula  $C_{24}H_{25}F_2N_3O_4$  M.Wt 457.47

Solubility  $\geq 45.7\text{mg/mL}$  in DMSO with ultrasonic Storage Store at  $-20^{\circ}\text{C}$

General tips For obtaining a higher solubility, please warm the tube at  $37^{\circ}\text{C}$  and shake it in the ultrasonic bath for a while. Stock solution can be stored below  $-20^{\circ}\text{C}$  for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



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

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### Protocol

**Cell experiment:** Cells are exposed to AZD8186 at concentrations ranging from 3 to 0.01  $\mu$ M 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  $\beta$ -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].

**Animal experiment:** 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<sup>3</sup>) 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.

### References:

[1]. Hancox U, et al. Inhibition of PI3K $\beta$  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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### Background

#### Description:

IC<sub>50</sub>: 0.003  $\mu$ M for PI3K $\beta$  and 0.017  $\mu$ M for PI3K $\delta$

The PI3K-Akt signaling pathway plays a critical role in cell growth, proliferation, motility, and survival. In human cancer, this pathway is activated by several mechanisms, including somatic mutations, deletions, and amplifications. Class I PI3Ks are further divided into class IA enzymes (PI3K $\alpha$ , PI3K $\beta$ , and PI3K $\delta$ ) and class IB enzymes (PI3K $\gamma$ ). AZD8186 is a potent and selective inhibitor of PI3K $\beta$  and PI3K $\delta$ .

In vitro: AZD8186 gave potent inhibition of p-Akt in cells sensitive to PI3K $\beta$  inhibition and in cells sensitive to PI3K $\delta$  inhibition but not to cells sensitive to PI3K $\alpha$  inhibition. The overall kinase selectivity of AZD8186 was evaluated in several panels of recombinant protein and lipid kinase assays. 13 did not show significant activity against a panel of 59 protein kinases tested at 1  $\mu$ M [1].

In vivo: The antitumor activity of AZD8186 was evaluated in the PTEN deficient PC3 prostate tumor xenograft model in nude mice, either at 100 mg/kg b.i.d. without ABT coadministration, or at 60, 30, and 10 mg/kg b.i.d. with ABT coadministration. Higher inhibition was seen in the 60 and 30 mg/kg groups with ABT coadministration than in the 100 mg/kg group without ABT coadministration [1].

Clinical trial: AZD8186 was selected as a clinical candidate for treatment of PTEN-deficient cancers and has recently entered phase I clinical trials [2].

#### Reference:

[1] Barlaam B, Cosulich S, Degorce S, Fitzek M, Green S, Hancox U, Lambert-van der Brempt C, Lohmann JJ, Maudet M, Morgentin R, Pasquet MJ, Péru A, Plé P, Saleh T, Vautier M, Walker M, Ward L, Warin N. Discovery of (R)-8-(1-(3,5-difluorophenylamino)ethyl)-N,N-dimethyl-2-morpholino-4-oxo-4H-chromene-6-carboxamide (AZD8186): a potent and selective inhibitor of PI3K $\beta$  and PI3K $\delta$  for the treatment of PTEN-deficient cancers. J Med Chem. 2015 Jan 22;58(2):943-62.

[2] <https://clinicaltrials.gov/ct2/show/NCT01884285?term=AZD8186&rank=1>

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