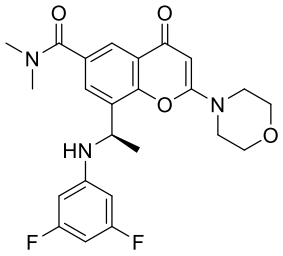
Product data sheet

MedKoo Cat#: 406260 Name: AZD8186 CAS#: 1627494-13-6 Chemical Formula: $C_{24}H_{25}F_2N_3O_4$ Exact Mass: 457.18131 Molecular Weight: 457.4	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

AZD8186 is and inhibitor of the beta isoform of phosphoinositide-3 kinase (PI3K), with potential antineoplastic activity. Upon administration, PI3Kbeta inhibitor AZD8186 selectively inhibits the activity of PI3Kbeta in the PI3K/Akt/mTOR signaling pathway, which may result in a decrease of tumor cell proliferation. It also induces cell death in PI3K-expressing cancer cells. By specifically targeting class I PI3K beta, this agent may be more efficacious and less toxic than pan PI3K inhibitors. PI3K-mediated signaling is often dysregulated in cancer cells and contributes to increased tumor cell growth, survival, and tumor resistance to a variety of antineoplastic agents. AZD8186 is currently under Phase I clinical trials.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	63.0	137.74
DMF	3.0	6.56
Ethanol	35.0	76.52

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.19 mL	10.93 mL	21.86 mL
5 mM	0.44 mL	2.19 mL	4.37 mL
10 mM	0.22 mL	1.09 mL	2.19 mL
50 mM	0.04 mL	0.22 mL	0.44 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Schwartz S, Wongvipat J, Trigwell CB, Hancox U, Carver BS, Rodrik-Outmezguine V, Will M, Yellen P, de Stanchina E, Baselga J, Scher HI, Barry ST, Sawyers CL, Chandarlapaty S, Rosen N. Feedback suppression of PI3Kα signaling in PTEN-mutated tumors is relieved by selective inhibition of PI3Kβ. Cancer Cell. 2015 Jan 12;27(1):109-22. doi: 10.1016/j.ccell.2014.11.008. Epub 2014 Dec 24. PMID: 25544636; PMCID: PMC4293347.

In vivo study

1. Lynch JT, Polanska UM, Delpuech O, Hancox U, Trinidad AG, Michopoulos F, Lenaghan C, McEwen R, Bradford J, Polanski R, Ellston R, Avivar-Valderas A, Pilling J, Staniszewska A, Cumberbatch M, Critchlow SE, Cruzalegui F, Barry ST. Inhibiting PI3Kβ with AZD8186 Regulates Key Metabolic Pathways in PTEN-Null Tumors. Clin Cancer Res. 2017 Dec 15;23(24):7584-7595. doi: 10.1158/1078-0432.CCR-17-0676. Epub 2017 Oct 2. PMID: 28972046.

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7. Bioactivity

Biological target:

AZD8186 is a PI3K inhibitor, which potently inhibits PI3Kβ (IC50=4 nM) and PI3Kδ (IC5050=12 nM) with selectivity over PI3Kα (IC50=35 nM) and PI3Kγ (IC50=675 nM).

In vitro activity

The increase in expression of IGF1R is accompanied by increased expression of the IRS1 protein in LNCaP (1.5-fold after one hour, 2.8-fold in 6 hours) and BT-549 cells (1.9-fold induction after 4 hours) (Figure 3C and S3K). In both models, mTOR activation is dependent on PI3Kβ, as demonstrated by the sensitivity of S6K phosphorylation to AZD8186 (Figure 3C, S3K). Activated S6K phosphorylates serine sites of IRS1 (S312 and/or S636/639) that causes the degradation of IRS1. Increased IRS1 expression in cells treated with AZD8186 was associated with decreased phosphorylation of IRS1 S636/639 and increased phosphorylation at Y612, a site that plays a role in the ability of IRS1 to activate PI3K (Figure 3C, S3K). These data suggest that inhibition of PI3Kβ relieves feedback inhibition of IGF and insulin signaling by increasing IGF1R and IRS1 expression and thus causing reactivation of PI3Kα.

Reference: Cancer Cell. 2015 Jan 12; 27(1): 109–122. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293347/

In vivo activity

Treating 786-0 tumor mice xenografts, a PTEN-null renal cell adenocarcinoma cell line, with AZD8186 results in significant antitumor activity (Fig. 4A), and changes in FDG-PET uptake. This tumor is sensitive to AZD8186 at doses as low as 12.5 mg/kg. Examination of pathway biomarkers in this model showed that in addition to inhibition of pAKT, pPRAS40, pNDRG1, and pS6, downregulation of HMGCS1 and IDI1 was observed (Fig. 4B). These in vivo observations were consistent in vitro; expression of HMGCS1 was downregulated in 2D and 3D cultures. However, the degree of downregulation was greater in 3D and correlated with growth suppression (Supplementary Fig. S8A). 786-0 cells were insensitive to AZD8186 when grown in 2D, but sensitive in 3D culture conditions (Supplementary Fig. S8B). Although the effects in tumor models can vary between models, modulation of the cholesterol pathway is evident when AZD8186 delivers antitumor benefit.

Reference: Clin Cancer Res. 2017 Dec 15;23(24):7584-7595. https://clincancerres.aacrjournals.org/content/23/24/7584.long

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.