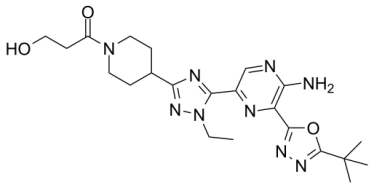
Data Sheet

Product Name:	AZD-8835
Cat. No.:	CS-4984
CAS No.:	1620576-64-8
Molecular Formula:	C22H31N9O3
Molecular Weight:	469.54
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
Solubility:	DMSO : 16 mg/mL (34.08 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

AZD8835 is a potent and selective inhibitor of **PI3Kα** and **PI3Kδ** with **IC_{50}**s of 6.2 and 5.7 nM, respectively. IC50 & Target: IC50: 6.2 nM (PI3Kα), 431 nM (PI3Kβ), 6 nM (PI3Kα-E545K), 5.8 nM (PI3Kα-H1047R), 5.7 nM (PI3Kδ), 90 nM (PI3Kγ)[1] **In Vitro:** The selectivity profile of AZD8835 (Compound 25) among the class I PI3K isoforms is tested in enzyme and cell based assays. At the enzyme level, AZD8835 is a potent mixed inhibitor of PI3Kα (IC_{50} 6.2 nM) and PI3Kδ (IC_{50} 5.7 nM), with selectivity against PI3Kβ (IC_{50} 431 nM) and PI3Kγ (IC_{50} 90 nM). AZD8835 is also a potent inhibitor of the commonly occurring PI3Kα mutants, PI3Kα- E545K (IC_{50} 6 nM) and PI3Kα-H1047R (IC_{50} 5.8 nM). In cell-based assays assessing the ability to inhibit Akt phosphorylation, AZD8835 is a potent inhibitor in cells sensitive to PI3Kα inhibition (IC_{50} 57 nM in PIK3CA mutant human breast ductal carcinoma BT474 cell line) and in cells sensitive to PI3Kδ inhibition (IC_{50} 49 nM in Jeko-1 B cell line, but not to cells sensitive to PI3Kβ inhibition (IC_{50} 3.5 μM in PTEN null breast adenocarcinoma MDA-MB-468 cells) or to PI3Kγ inhibition (IC_{50} 530 nM in monocytic RAW264 cell line)[1]. **In Vivo:** AZD8835 (Compound 25) displays good solubility, good permeability and low turnover in hepatocytes from various species. As expected from the in vitro data, low in vivo clearance associated with high bioavailability is seen in both rat and dog. AZD8835 shows high exposure following oral administration to SCID mice (AUC: 137 μM.h and C_{max} 34 μM at 50 mg/kg p.o.) and is selected for further in vivo evaluation. In a pharmacodynamic experiment following chronic oral dosing (25 mg/kg b.i.d. or 6 mg/kg b.i.d. of AZD8835) in nude mice bearing mutant H1047R PI3Kα SKOV-3 tumour xenografts, target modulation is assessed by measuring Akt phosphorylation levels at Ser473 at 30 minutes and 8 hours. At both doses, strong inhibition of Akt phosphorylation is observed at the 30 minute timepoint. At 8 hours, significant inhibition is still seen at the 25 mg/kg dose, whereas no inhibition is seen at the lower dose of 6 mg/kg, consistent with the lower plasma concentrations observed[1].

References:

[1]. Barlaam B, Discovery of 1-(4-(5-(5-amino-6-(5-tert-butyl-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-1-ethyl-1,2,4-triazol-3-yl)piperidin-1-yl)-3-hydroxypropan-1-one (AZD8835): A potent and selective inhibitor of PI3Kα and PI3Kδ for the treatment of cancers. Bioorg Med Chem Lett. 2015 Nov 15;25(22):5155-62.

CAIndexNames:

1-Propanone, 1-[4-[5-[5-amino-6-[5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2-yl]-2-pyrazinyl]-1-ethyl-1H-1,2,4-triazol-3-yl]-1-piperidinyl]-3-hydroxy-

SMILES:

O=C(N1CCC(C2=NN(CC)C(C3=NC(C4=NN=C(C(C)(C)C)O4)=C(N)N=C3)=N2)CC1)CCO

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

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