AZD 6482

Cat. No.: HY-10344

CAS No.: 1173900-33-8

Molecular Formula: $C_{22}H_{24}N_4O_4$

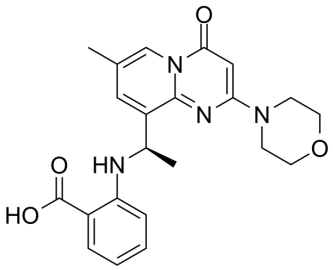
Molecular Weight: 408.45

Target: PI3K; Autophagy

Pathway: PI3K/Akt/mTOR; Autophagy

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 : 50 mg/mL (122.41 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4483 mL	12.2414 mL	24.4828 mL
5 mM	0.4897 mL	2.4483 mL	4.8966 mL
10 mM	0.2448 mL	1.2241 mL	2.4483 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.12 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.12 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AZD 6482 (KIN-193) is a potent and selective p110β inhibitor with an IC_{50} of 0.69 nM.

IC_{50} & Target

PI3Kβ 0.69 nM (IC_{50})	PI3Kδ 13.6 nM (IC_{50})	PI3Kγ 47.8 nM (IC_{50})	PI3Kα 136 nM (IC_{50})
PI3K-C2β 54.1 nM (IC_{50})	hVps34 3390 nM (IC_{50})	DNA-PK 53.7 nM (IC_{50})	mTOR 3930 nM (IC_{50})
PI4Kα 8830 nM (IC_{50})	Autophagy		

In Vitro	An in vitrokinase assay demonstrates that AZD 6482 (KIN-193) is highly potent in the inhibition of p110β's kinase activity (IC_{50} of 0.69 nM) and has 200, 20, and 70-fold selectivity over p110α, p110δ, and p110γ isoforms, respectively. AZD 6482 also exhibits selectivity of ~80 fold over PI3K-C2β and DNA-PK and more than 1,000-fold over other phosphatidylinositol-3 kinase–related kinases (PIKKs). An inhibitor-kinase interaction profiling of AZD 6482 against a panel of 433 kinases using the KinomeScan approach demonstrates that AZD 6482 is highly selective in its interaction with PI3Ks. To determine whether AZD 6482 selectively targets PTEN-deficient tumors, the effect of AZD 6482 is tested on cell proliferation on a large panel of 422 cancer cell lines using high-throughput tumor cell line profiling. 35% of cell lines with PTEN mutations (20 out of 57) and 16% of cell lines with wild-type PTEN (58 out of 365) are sensitive to AZD 6482 with a threshold of EC_{50}<5 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	To determine the pharmacodynamics of AZD 6482 (KIN-193) in tumors in vivo, rat fibroblast (Rat1) cells are engineered to express both p53DD, a dominant negative mutant of p53, and a constitutively activated myr-p110β (Rat1-CA-p110β) to enable these cells to form xenograft tumors in mice. For comparison, an isogenic Rat1 cell line expressing p53DD and myr-p110α (Rat1-CA-p110α) is also generated. Rat1-CA-p110α and Rat1-CA-p110β cells are introduced subcutaneously into the contralateral flanks of athymic mice such that tumors driven by activated p110α or p110β would be exposed to identical conditions and that concern about animal-to-animal variability could be eliminated. When tumors reach a volume of ~500 mm^3, the tumor-bearing mice receives a single IP injection of AZD 6482 (10 mg/kg). The plasma concentration of AZD 6482 is highest at 1 hour post-injection and declined to undetectable levels by 4h. Concentrations of AZD 6482 in both the CA-p110 α- and CA-p110β-driven tumors parallel the plasma concentrations. Analyses of tumor lysates harvested at various time points after AZD 6482 injection reveal that the phosphorylation of AKT is significantly reduced at 1hour after AZD 6482 injection in Rat1-CA-p110β tumors, but remain unchanged in Rat1-CAp110α tumors[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	AZD 6482 (KIN-193) is profiled at a concentration of 10 μM against a diverse panel of 433 kinases. Scores for primary screen hits are reported as percent of the DMSO control (% control). For kinases where no score is shown, no measurable binding is detected. The lower the score, the lower the K_d is likely to be, such that scores of zero represent strong hits. Scores are related to the probability of a hit, but are not strictly an affinity measurement. At a screening concentration of 10 μM, a score of less than 10% implies that the false positive probability is less than 20% and the K_d is most likely less than 1 μM. A score between 1-10% implies that the false positive probability is less than 10%, although it is difficult to assign a quantitative affinity from a single-point primary screen. A score of less than 1% implies that the false positive probability is less than 5% and the K_d is most likely less than 1 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	Cell viability is determined. Briefly, cells are seeded in medium containing 5% FBS at a density insuring cell growth throughout drug treatment (~15% for most cell lines). Drug treatment is started 24 h post seeding and continued for 72 h. Cell are fixed and stained using Syto60, a red fluorescent DNA stain. The relative cell number is calculated by taking the ratio of the relative fluorescence intensity from drug treated wells over untreated wells after background subtraction (cells-free wells). Nine doses of AZD 6482 (KIN-193) are used in 2-fold dilution steps ranging from 5.12 μM to 0.02 μM. IC_{50}, corresponding to 50% cell number compared to control (untreated) wells, is determined using a fixed top and bottom sigmoidal fitting algorithm implemented in PipelinePilot[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Approximately 6-8 week-old female nude mice are injected s.c. with Rat1-Myr-HA-p110α(Rat1-CAp110α) cells ($1×10^6$ cells in 40% matrigel) in one flank (site 1) and Rat1-Myr-HA-p110β (Rat1-CAp110β) cells ($0.5×10^6$ cells in 10% matrigel) in the contralateral flank (site 2). When tumors grow to ~500 mm^3, mice are dosed once by ip injection with AZD 6482 formulated in 7.5% NMP, 40% PEG400, 52.5% dH_2O at 0.1 mL/10g body weight and 10 mg/kg. Tumors are collected at 0, 1, 4, 8, and 24 h following compound administration and blood samples are obtained by direct heart puncture. Serum is separated and stored at -80°C. The drug concentrations in serum and tumor samples are assessed by LC-MS/MS analysis by the DMPK group.

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

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Cell Discov. 2016 Sep 20;2:16030.
- Cancer Discov. 2012 May;2(5):425-33.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2015 Oct 7;6:8501.

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REFERENCES

[1]. Ni J, et al. Functional characterization of an isoform-selective inhibitor of PI3K-p110β as a potential anticancer agent. Cancer Discov. 2012 May;2(5):425-33.

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