PKI-402

Cat. No.: HY-10683

CAS No.: 1173204-81-3

Molecular Formula: $C_{29}H_{34}N_{10}O_3$

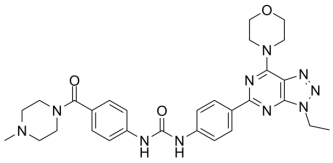
Molecular Weight: 570.65

Target: PI3K; mTOR

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 : 5 mg/mL (8.76 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7524 mL	8.7619 mL	17.5239 mL
5 mM	0.3505 mL	1.7524 mL	3.5048 mL
10 mM	---	---	---

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 1.43 mg/mL (2.51 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

PKI-402 is a selective, reversible, ATP-competitive inhibitor of PI3K, including PI3K-α mutants, and mTOR (IC_{50}=2, 3, 7,14 and 16 nM for PI3Kα, mTOR, PI3Kβ, PI3Kδ and PI3Kγ).

IC_{50} & Target

PI3Kα 2 nM (IC_{50})	PI3Kα-H1047R 3 nM (IC_{50})	PI3Kα-E545K 3 nM (IC_{50})	PI3Kβ 7 nM (IC_{50})
PI3Kδ 14 nM (IC_{50})	PI3Kγ 16 nM (IC_{50})	mTOR 3 nM (IC_{50})	

In Vitro

PKI-402 is an equipotent inhibitor of class I PI3K, including the E545K and H1047R PI3K-α mutants (IC_{50}=2, 3 and 3 nM for PI3Kα, PI3Kα-H1047R and PI3Kα-E545K, respectively). PKI-402 causes in vitro growth inhibition of human tumor cell lines

	derived from a diverse set of human tumor tissues, including breast, brain (glioma), pancreas, and non-small cell lung cancer (NSCLC) tissues. PKI-402 inhibits MDA-MB-361 [breast: $Her2^+$ and PIK3CA mutant (E545K)], with an IC_{50} of 6 nM. PKI-402 inhibits HCT116 (K-Ras and PIK3CA mutant) with an IC_{50} of 33 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PKI-402 displays antitumor activity (i.v. route) in breast [MDA-MB-361: $Her2^+$ and PIK3CA (E545K)], glioma (U87MG and PTEN), and NSCLC (A549; K-Ras and STK11) xenograft models. PKI-402 causes regression in the MDA-MB-361 xenograft model. PKI-402 effect is most pronounced at 100 mg/kg (daily for 5 days, one round), which reduces initial tumor volume and prevents tumor re-growth for 70 days. In MDA-MB-361 tumor tissue, PKI-402 at 100 mg/kg (single dose) fully suppresses p-Akt at both the T308 and the S473 sites at 8 hours and induces cleaved PARP. At 24 hours, p-Akt suppression is still evident, as is cleaved PARP[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Enzyme assays are done in fluorescent polarization (FP) format. Human class I PI3Ks and PI3K-α mutants (E545K and H1047R) are produced in Sf9. GST-GRP1 (murine) is produced in Escherichia coli and isolated by GST-Sepharose. Assay buffers are reaction buffer [20 mM HEPES (pH 7.1), 2 mM $MgCl_2$, 0.05% CHAPS, and 0.01% β-mercaptoethanol] and stop/detection buffer [100 mM HEPES (pH 7.5), 4 mM EDTA, 0.05% CHAPS]. FP reaction is run for 30 min at room temperature in 20 μL of reaction buffer containing 20 μM phosphatidylinositol 4,5-bisphosphate (PIP2), 25 μM ATP, and <4% DMSO (compound solvent). FP reaction is stopped with 20 μL of stop/detection buffer (10 nM probe and 40 nM GST-GRP), and after 2 h, data are collected. Selectivity of PKI-402 is evaluated in the 236 human kinase panel at [ATP]=K_m for each enzyme[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	MDA-MB-361, MDA-MB-468, T47D, MCF7, BT474, HT29, HCT116, DLD1, U87MG, H157, NCI-H460, A549, NCI-H1975, NCI-H1650, NCI-H2170, KB, 786-0, A498, MIA-PaCa-2, and PC3 cell lines are propagated at 37°C in 5% CO_2 incubators in supplier-recommended growth medium. Cell growth inhibition is determined using the CellTiter 96 AQueous proliferation assay. Data are collected after 72 h using a Wallac Victor2 V 1420 multilabel HTS counter. FOXO-GFP translocation in U2OS cells is quantified after 60-min PKI-402 exposure using a Cellomics ArrayScan VTI Reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] PKI-402 or vehicle is administered by i.v. route. Nude mice bearing MDA-MB-361 tumors are used. Tumor weight is calculated. Pharmacodynamic (biomarker) measurements are done on tumor-bearing female nude mice administered PKI-402. Tumor or normal tissue samples are collected from euthanized animals, homogenized, washed twice with cold (4°C) PBS, and then treated with cell lysis buffer[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cell Prolif. 2019 May;52(3):e12609.
- Int Immunopharmacol. 2023 Aug 13;123:110793.
- Sci Rep. 2022 Apr 12;12(1):6090.
- Molecules. 2020 Apr 23;25(8):1980.

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REFERENCES

[1]. Mallon R et al. Antitumor efficacy profile of PKI-402, a dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor. Mol Cancer Ther. 2010 Apr;9(4):976-84.

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