Paxalisib

Cat. No.: HY-19962

CAS No.: 1382979-44-3

Molecular Formula: $C_{18}H_{22}N_8O_2$

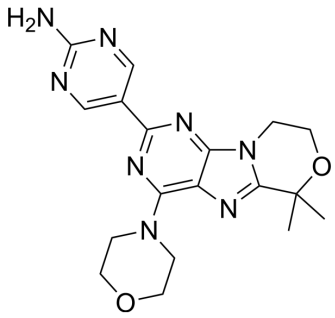
Molecular Weight: 382.42

Target: PI3K; mTOR

Pathway: PI3K/Akt/mTOR

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 7.69 mg/mL (20.11 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6149 mL	13.0746 mL	26.1493 mL
	5 mM	0.5230 mL	2.6149 mL	5.2299 mL
	10 mM	0.2615 mL	1.3075 mL	2.6149 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: 1 mg/mL (2.61 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 1 mg/mL (2.61 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1 mg/mL (2.61 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Paxalisib (GDC-0084) is a brain penetrant inhibitor of PI3K and mTOR, with K_is of 2 nM, 46 nM, 3 nM, 10 nM and 70 nM for PI3K α PI3Kβ, PI3Kδ, PI3Kγ and mTOR, respectively[1].

IC_{50} & Target

PI3Kα	PI3Kδ	PI3Kγ	PI3Kβ
2 nM (Ki)	3 nM (Ki)	10 nM (Ki)	46 nM (Ki)

mTOR
70 nM (Ki)

In Vitro	Paxalisib (GDC-0084; Compound 16) maintains inhibition of each of the Class I PI3K isoforms but with more potent inhibition of mTOR. Paxalisib is also tested in five different GBM cell lines and is found to have antiproliferative EC_{50}s ranging from 0.3 to 1.1 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	After a 25 mg/kg dose of Paxalisib (GDC-0084; Compound 16) administered orally, pAKT in normal mouse brain tissue is significantly inhibited at 1 and 6 h postdose. The potent inhibition of pAKT at both time points in this study demonstrates that Paxalisib inhibits its target behind a fully intact BBB. In addition to the pharmacodynamic effect in normal brain tissue, Paxalisib is studied in a subcutaneous U87 tumor xenograft model of glioblastoma in mice. In this study, Paxalisib achieves significant and dose-dependent tumor growth inhibition. Tumor growth inhibition is first observed at a 2.2 mg/kg dose level. Higher doses led to greater tumor growth inhibition, including tumor regressions at the 17.9 mg/kg dose level. Each of these doses is well tolerated for the duration of the study[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] PTEN-null U-87 MG/M human glioblastoma cancer cells are cultured in RPMI 1640 media plus 1% L-glutamine with 10% fetal bovine serum. Cells in log-phase growth are harvested and resuspended in HBSS:Matrigel (1:1, v:v) for injection into female NCr nude mice aged 20 weeks. Animals receive five million cells subcutaneously in the right lateral thorax in 0.1 mL. Mice bearing established tumors in the range of 200-500 mm^3 are separated into groups of equally sized tumors (n=6-7/group) to receive escalating doses of Paxalisib. Paxalisib is formulated once weekly in 0.5% methylcellulose and 0.2% Tween-80 at concentrations needed for target doses in a volume of 0.2 mL. All formulations are stored in a refrigerator and brought to room temperature and mixed well by vortex before oral administration by gavage once daily for 23 days. Tumor volumes are calculated. Changes in body weights are reported as a percentage change from the starting weight. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.
- Biochem Biophys Res Commun. 2018 Sep 10;503(3):1941-1948.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. Heffron TP, et al. Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. ACS Med Chem Lett. 2016 Feb 16;7(4):351-6.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA