Voxtalisib

Cat. No.: HY-15900

CAS No.: 934493-76-2

Molecular Formula: $C_{13}H_{14}N_6O$

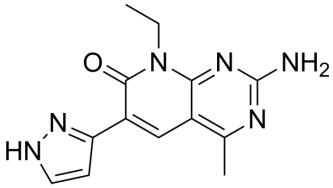
Molecular Weight: 270.29

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 : 10 mg/mL (37.00 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	3.6997 mL	18.4986 mL	36.9973 mL
	5 mM	0.7399 mL	3.6997 mL	7.3995 mL
	10 mM	0.3700 mL	1.8499 mL	3.6997 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 (3.70 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (3.70 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1 mg/mL (3.70 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Voxtalisib (XL765) is a potent PI3K inhibitor, which has a similar activity toward class I PI3K (IC_{50}s=39, 113, 9 and 43 nM for p110α, p110β, p110γ and p110δ, respectively), also inhibits DNA-PK (IC_{50}=150 nM) and mTOR (IC_{50}=157 nM). Voxtalisib (XL765) inhibits mTORC1 and mTORC2 with IC_{50}s of 160 and 910 nM, respectively.

IC_{50} & Target

p110γ 9 nM (IC_{50})	p110α 39 nM (IC_{50})	p110δ 43 nM (IC_{50})	p110β 113 nM (IC_{50})
mTOR	mTORC1	mTORC2	DNA-PK

	157 nM (IC_{50})	160 nM (IC_{50})	910 nM (IC_{50})	150 nM (IC_{50})

In Vitro

Voxtalisib (XL765) displays potent inhibitory activity against class I PI3K isoforms p110α, p110β, p110δ, and p120γ, with IC_{50}s of 39, 110, 43, and 9 nM, respectively. The IC_{50} value for inhibition of PI3Kα by Voxtalisib is determined at various concentrations of ATP, revealing Voxtalisib be an ATP-competitive inhibitor with an equilibrium inhibition constant (K_i) value of 13 nM. Voxtalisib also inhibits mTOR (IC_{50}s of 160 and 910 nM for mTORC1 and mTORC2, respectively) in an immune-complex kinase assay and the PI3K-related kinase DNA-PK (IC_{50} value of 150 nM). In contrast, Voxtalisib (XL765) has relatively weak inhibitory activity toward the class III PI3K vacuolar sorting protein 34 (VPS34; IC_{50} value of ~9.1 μM). Consistent with its inhibitory activity against purified PI3K proteins, SAR245409 inhibits EGF-induced PIP_3 production in PC-3 and MCF7 cells with IC_{50}s of 290 and 170 nM, respectively. The ability of Voxtalisib to inhibit phosphorylation of key signaling proteins downstream of PI3K is examined by assessing its effects on EGF-stimulated phosphorylation of AKT and on nonstimulated phosphorylation of S6 in PC-3 cells by cell-based ELISA. Voxtalisib inhibits these activities with IC_{50}s of 250 and 120 nM, respectively. In MCF7 and PC-3 cells, Voxtalisib inhibits proliferation (monitored by BrdUrd incorporation) with IC_{50}s of 1,070 and 1,840 nM, respectively. To further characterize the effects of Voxtalisib on tumor cell growth, an assay monitoring the anchorage-independent growth of PC-3 and MCF7 cells in soft agar over a 14-day period is used. SAR245409 inhibits colony growth with an IC_{50} value of 270 nM in PC-3 cells and 230 nM in MCF7 cells[2].

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

In Vivo

Oral administration of Voxtalisib (XL765) causes a dose-dependent decrease of phosphorylation of AKT, p70S6K, and S6 in the tumors, reaching a maximum of 84% inhibition of S6 phosphorylation at 30 mg/kg at 4 hours. The dose-response relationships derive from the 4 hours time point predict 50% inhibition of AKT, p70S6K, and S6 phosphorylation to occur at doses of 19 mg/kg ($pAKT^{T308}$ and $pAKT^{S473}$), 51 mg/kg (p-p70S6K), and 18 mg/kg (pS6). Inhibition of AKT, p70S6K, and S6 phosphorylation in MCF7 tumors following a 30 mg/kg dose of Voxtalisib is maximal at 4 hours, reaching 61% to 84%; however, the level of inhibition decreases to 0% to 42% by 24 hours, and minimal or no inhibition is evident by 48 hours. Following a 100 mg/kg dose of Voxtalisib, inhibition is also maximal at 4 hours (52%-75%)[2].

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

PROTOCOL

Cell Assay [2]

Cellular proliferation is assessed using the Cell Proliferation ELISA, Bromodeoxyuridine Chemiluminescence Kit. Cytotoxicity is assessed using the ATP Bioluminescence Assay as follows: PC-3, MCF7, A549, LS174T, MDA-MB-468, U87-MG, and OVCAR-3 cells are plated at densities of 7×10^3, 1.5×10^4, 6×10^3, 7×10^3, 7×10^3, 6×10^3, 1.5×10^4 cells per well, respectively, onto 96-well microtiter plates in culture medium, incubated at 37°C, 5% CO_2 for 18 hours, and then treated with a serial dilution of compound in medium containing a final concentration of 0.3% DMSO. Triplicate wells are used for each compound concentration. Control wells receive 0.3% DMSO in media. Cultures are incubated at 37°C, 5% CO_2 for an additional 24 hours and cells are then assayed for viability using the ViaLight HS Kit[2].

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

Animal Administration [2]

Mice[2]

In vivo efficacy studies are performed in athymic nude mice. Tumor cells are cultured in DMEM supplemented with 10% FBS (20% for PC-3 and OVCAR-3 cells), Penicillin-Streptomycin, and nonessential amino acids at 37°C in a humidified 5% CO_2 atmosphere. On day 0, cells are harvested by brief trypsinization, and 1 to 5×10^6 cells in 0.1 mL ice-cold Hanks Balanced Salt Solution are implanted subcutaneously (OVCAR-3) or intradermally (MCF7 and U-87 MG) into the hind flank of female athymic nude mice. In the case of the MCF7 model, an estrogen pellet (IRA) is implanted subcutaneously at the nape of neck at the time of tumor cell implantation. A total of 3×10^6 PC-3 cells are similarly harvested and implanted subcutaneously into the hind-flank of 5- to 8-week-old male nude mice. Tumor growth is monitored weekly with calipers until staging and dose initiation. During the dosing period, body and tumor weights are assessed. Voxtalisib (XL-765) is formulated in sterile water/10 mM HCl or water and administered at the indicated doses and regimens by oral gavage at a dose volume of 10 mL/kg.

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.
- Acta Neuropathol. 2019 Sep;138(3):443-456.
- Front Pharmacol. 2020 Nov 11;11:580407.
- Molecules. 2020 Apr 23;25(8):1980.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. Garcia-Echeverria C, et al. Drug discovery approaches targeting the PI3K/Akt pathway in cancer. Oncogene. 2008 Sep 18;27(41):5511-26.

[2]. Yu P, et al. Characterization of the activity of the PI3K/mTOR inhibitor XL765 (SAR245409) in tumor models with diverse genetic alterations affecting the PI3K pathway. Mol Cancer Ther. 2014 May;13(5):1078-91.

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