OTSSP167 hydrochloride

Cat. No.: HY-15512A

CAS No.: 1431698-10-0

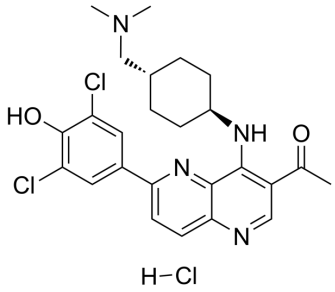
Molecular Formula: $C_{25}H_{29}Cl_3N_4O_2$

Molecular Weight: 523.88

Target: MELK

Pathway: PI3K/Akt/mTOR

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 2 years; -20°C, 1 year (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 33.33 mg/mL (63.62 mM; Need ultrasonic)
H_2O : 7.14 mg/mL (13.63 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9088 mL	9.5442 mL	19.0883 mL
5 mM	0.3818 mL	1.9088 mL	3.8177 mL
10 mM	0.1909 mL	0.9544 mL	1.9088 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: ≥ 3 mg/mL (5.73 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3 mg/mL (5.73 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 3 mg/mL (5.73 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: PBS
   Solubility: 1 mg/mL (1.91 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description OTSSP167 (OTS167) hydrochloride is a highly potent and ATP-competitive MELK inhibitor with IC_{50} value of 0.41 nM.

IC_{50} & Target IC50: 0.41 nM (MELK)

In Vitro OTSSP167 inhibits the growth of A549 (lung), T47D (breast), DU4475 (breast), 22Rv1 (prostate) and HT1197 (bladder) cancer cells with IC_{50} values of 6.7, 4.3, 2.3, 6.0 and 97 nM, respectively[1].

	OTSSP167 can abrogate the mitotic checkpoint, disrupt MCC and MCC-APC/C interaction in MCF7 cells. OTSSP167 causes GFP-MELK localization to cell cortex in prometaphase cells[2]. OTSSP167 is a MELK selective inhibitor, exhibits a strong in vitro activity, conferring an IC_{50} of 0.41 nM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	OTSSP167 (20 mg/kg, i.v.) results in tumor growth inhibition (TGI) of 73% in xenograft mouse model; OTSSP167 (1, 5, and 10 mg/kg, p.o.) reveals TGI of 51, 91, and 108%, respectively. OTSSP167 (20 mg/kg, p.o.) shows no tumor growth suppressive effect on PC-14 xenografts[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	For in vitro kinase assay, MELK recombinant protein (0.4 μg) is mixed with 5 μg of each substrate in 20 μL of kinase buffer containing 30 mM Tris-HCl (pH), 10 mM DTT, 40 mM NaF, 10 mM $MgCl_2$, 0.1 mM EGTA with 50 μM cold-ATP and 10 Ci of [γ-^{32}P]ATP for 30 min at 30°C. The reaction Is terminated by addition of SDS sample buffer and boiled for 5 min prior to SDS-PAGE. The gel is dried and autoradiographed with intensifying screens at room temperature. OTSSP167 (final concentration of 10 nM) is dissolved in DMSO and added to kinase buffer before the incubation. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	In vitro cell viability is measured by the colorimetric assay using Cell Counting Kit-8. Cells are plated in 100 μL in 96-well plates at a density that generates continual linear growth (A549, 1×10^3 cells; T47D, 3×10^3 cells; DU4475, 4×10^3 cells; 22Rv1, 6×10^3 cells; and HT1197, 2×10^3 cells, in 100 μL per well). The cells are allowed to adhere overnight before exposure to OTSSP167 for 72 hours at 37°C. Plates are read using a spectrophotometer at a wavelength of 450 nm. All assays are carried out in triplicate. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	MDA-MB-231 cells are injected into the mammary fat pads of NOD.CB17-Prkdc^{scid}/J mice. A549, MIAPaCa-2 and PC-14 cells (1×10^5 cells) are injected subcutaneously in the left flank of female BALB/cSLC-nu/nu mice. DU145 cells are injected subcutaneously in the left flank of male BALB/cSLC-nu/nu mice. When MDA-MB-231, A549, DU145, MIAPaCa-2, and PC-14 xenografts has reached an average volume of 100, 210, 110, 250, and 250 mm^3, respectively, animals are randomized into groups of 6 mice (except for PC-14, for which groups of 3 mice are used). For oral administration, OTSSP167 and other compounds are prepared in a vehicle of 0.5% methylcellulose and given by oral garbage at the indicated dose and schedule. For intravenous administration, compounds are formulated in 5% glucose and injected into the tail vein. An administration volume of 10 mL per kg of body weight is used for both administration routes. Tumor volumes are determined every other day using a caliper. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Mol Cancer. 2014 May 4;13:100.
- Blood Cancer J. 2019 Nov 18;9(12):87.
- Clin Cancer Res. 2018 Nov 15;24(22):5645-5657.
- EMBO Mol Med. 2018 Mar;10(3). pii: e8274.
- Neuro Oncol. 2020 Jan 11;22(1):58-69.

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REFERENCES

[1]. Chung S, Suzuki H, Miyamoto T, et al. Development of an orally-administrative MELK-targeting inhibitor that suppresses the growth of various types of human cancer. Oncotarget. 2012 Dec 21.

[2]. Ji W, et al. OTSSP167 Abrogates Mitotic Checkpoint through Inhibiting Multiple Mitotic Kinases. PLoS One. 2016 Apr 15;11(4):e0153518.

[3]. Cho YS, et al. The crystal structure of MPK38 in complex with OTSSP167, an orally administrative MELK selective inhibitor. Biochem Biophys Res Commun. 2014 Apr 25;447(1):7-11.

[4]. Jurmeister S, et al. Identification of potential therapeutic targets in prostate cancer through a cross-species approach. EMBO Mol Med. 2018 Feb 5. pii: e8274.

[5]. Meel MH, et al. MELK inhibition in Diffuse Intrinsic Pontine Glioma. Clin Cancer Res. 2018 Jul 30. pii: clincanres.0924.2018.

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