Onatasertib

Cat. No.: HY-16956

CAS No.: 1228013-30-6

Molecular Formula: $C_{21}H_{27}N_5O_3$

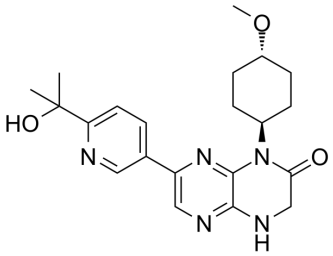
Molecular Weight: 397.47

Target: mTOR; Apoptosis

Pathway: PI3K/Akt/mTOR; Apoptosis

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 : ≥ 27 mg/mL (67.93 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5159 mL	12.5796 mL	25.1591 mL
5 mM	0.5032 mL	2.5159 mL	5.0318 mL
10 mM	0.2516 mL	1.2580 mL	2.5159 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: ≥ 1.25 mg/mL (3.14 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.25 mg/mL (3.14 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Onatasertib (CC-223) is a potent, selective, and orally bioavailable inhibitor of mTOR kinase, with an IC_{50} value for mTOR kinase of 16 nM. Onatasertib inhibits both mTORC1 and mTORC2.

IC_{50} & Target

mTOR 16 nM (IC_{50})	mTORC1	mTORC2	DNA-PK 0.84 μM (IC_{50})
PI3K-α 4 μM (IC_{50})			

In Vitro	Onatasertib is a potent, selective, and orally bioavailable inhibitor of mTOR kinase, demonstrating inhibition of mTORC1 (pS6RP and p4EBP1) and mTORC2 [pAKT(S473)] in cellular systems. Onatasertib is selective for mTOR kinase with >200-fold selectivity over the related PI3K-α (IC_{50}=4.0 μM). Of the PI3K related kinases tested, Onatasertib shows no significant inhibition of ATR or SMG1 and inhibits DNA-PK with an IC_{50} value of 0.84 μM. When screened in a single-point assay against a commercially available panel of 246 kinases, only three kinases other than mTOR are inhibited >80% at 10 μM by Onatasertib. Upon follow-up IC_{50} value determination, only two are inhibited by Onatasertib with IC_{50} values below 1 μM; FLT4 (0.651 μM) and cFMS (0.028 μM). The exquisite kinase selectivity of Onatasertib is confirmed upon evaluation in cellular systems using ActivX KiNavtiv profiling. Other than mTOR kinase, no kinase target is identified when HCT 116 or A549 cells are treated for 1 hour with 1 μM Onatasertib and assayed for kinase activity. Onatasertib shows a concentration-dependent reduction in each marker, with IC_{50} values of 31±2 nM for pS6RP, 405±47 nM for p4EBP1, and 11±10 nM for pAKT(S473) in western blot analysis. Inhibition of these pathway biomarkers is investigated in additional cell types from a variety of tissue origins. Onatasertib inhibits both mTORC1 (S6RP and 4EBP1) and mTORC2 [AKT(S473)] markers across the panel with IC_{50} ranges of 27 to 184 nM for pS6RP, 120 to 1,050 nM for p4EBP1 and 11 to 150 nM for pAKT(S473) [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The antitumor activity of Onatasertib in the PC-3 xenograft model is determined using a number of dosing paradigms. Onatasertib significantly inhibits PC-3 tumor growth in a dose- and schedule-dependent manner. Dosing at 10 or 25 mg/kg, once daily, results in 46% (P<0.001) and 87% (P<0.001) reduction in tumor volume, respectively. Similar dose dependency is observed with twice-daily dosing at 5 or 10 mg/kg, corresponding to 65% (P<0.001) and 80% (P<0.001) tumor volume reductions. All dose levels are tolerated in the once-daily and twice-daily dosing studies, with only the 25 mg/kg/d group showing any significant body weight loss. These mice lost approximately 10% of their initial body weight after 3 weeks of dosing[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Counter screen against 246 protein kinases is outsourced and completed at a fixed CC-223 concentration (10 μM). Follow-up IC_{50} value determinations for ephrin type-B receptor 3 kinase (EPHB3), colony stimulating factor 1 receptor tyrosine kinase (CSF1R or cFMS), and FMS-related tyrosine kinase 4 (FLT4) are outsourced to Invitrogen[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	For other cell panel proliferation assays, CC-223 (1 nM, 100 nM and 1 μM) is spotted via an acoustic dispenser (EDC ATS-100) into an empty 384-well plate. Cells are diluted to desired densities and added directly to the compound-spotted plates. Cells are allowed to grow for 72 hours. Viability is assessed via Cell Titer-Glo. All data are normalized and represented as a percentage of the DMSO-treated cells. Results are then expressed as GI_{50} and/or IC_{50} values[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female 6- to 8-weeks-old CB17 SCID mice are inoculated s.c. with 2×10^6 PC-3 cells. When tumors reach approximately 125 mm^3, mice are randomized and treated once daily, twice daily, or every 2 days orally with vehicle or various doses of CC-223, at a dose volume of 5 mL/kg. The twice-daily doses are administered with a 10 hours separation between the morning and evening doses. Tumor volumes are determined before the initiation of treatment and are considered as the starting volumes. Tumors are measured twice a week for the duration of the study. The long and short axes of each tumor are measured using a digital caliper in millimeters. The tumor volumes are calculated. The tumor volumes are expressed in cubic millimeters (mm^3). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.
- Oncotarget. 2017 May 10;8(35):58469-58479.

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REFERENCES

[1]. Mortensen DS, et al. CC-223, a Potent and Selective Inhibitor of mTOR Kinase: In Vitro and In Vivo Characterization. Mol Cancer Ther. 2015 Jun;14(6):1295-305.

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