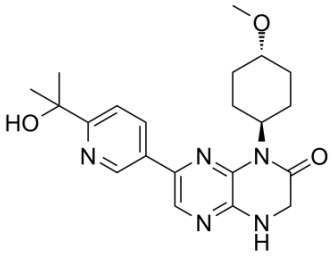
CC-223

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 6 months -20°C 1 month



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.

BIOLOGICAL ACTIVITY

Description

CC-223 is a potent, selective, and orally bioavailable inhibitor of mTOR kinase, with an IC_{50} value for mTOR kinase of 16 nM. CC-223 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

CC-223 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. CC-223 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, CC-223 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 CC-223. Upon follow-up

	IC_{50} value determination, only two are inhibited by CC-223 with IC_{50} values below 1 μM; FLT4 (0.651 μM) and cFMS (0.028 μM). The exquisite kinase selectivity of CC-223 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 CC-223 and assayed for kinase activity. CC-223 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. CC-223 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 CC-223 in the PC-3 xenograft model is determined using a number of dosing paradigms. CC-223 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, 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.

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