CC-115

Cat. No.: HY-16962

CAS No.: 1228013-15-7

Molecular Formula: $C_{16}H_{16}N_8O$

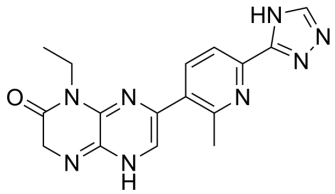
Molecular Weight: 336.35

Target: DNA-PK; mTOR

Pathway: Cell Cycle/DNA Damage; 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 : 20 mg/mL (59.46 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.9731 mL	14.8655 mL	29.7309 mL
5 mM	0.5946 mL	2.9731 mL	5.9462 mL
10 mM	0.2973 mL	1.4865 mL	2.9731 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: ≥ 2 mg/mL (5.95 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2 mg/mL (5.95 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CC-115 is a potent and dual DNA-PK and mTOR kinase inhibitor with IC_{50}s of 13 nM and 21 nM, respectively. CC-115 blocks both mTORC1 and mTORC2 signaling.

IC_{50} & Target

DNA-PK 13 nM (IC_{50})	mTOR 21 nM (IC_{50})	mTORC1	mTORC2
PI3Kα 852 nM (IC_{50})			

In Vitro

CC-115 inhibits PC-3 cells proliferation with an IC_{50} of 138 nM. In a kinase selectivity assessment against a panel of 250

	protein kinases at 3 μM, only one kinase other than mTOR kinase is identified with more than 50% inhibition (cFMS 57%, IC_{50} =2.0 μM). Of the PI3K related kinases (PIKKs) tested, CC-115 proves to be equipotent against DNA PK (IC_{50}=15 nM) and demonstrates 40 to >1000 fold selectivity against the remaining PIKKs tested; PI3K-alpha (IC_{50}=0.85 μM), ATR (50% inhibition at 30 μM) and ATM (IC_{50}>30 μM). The IC_{50} values for CC-115 are >10 μM against a panel of CYP enzymes and >33 μM for the hERG (human ether-a-go-go-related gene) ion channel. When screened in a single point assay at 10 μM against a Cerep receptor and enzyme panel only one target is inhibited >50% (PDE3, IC_{50}=0.63 μM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CC-115 shows good in vivo PK profiles across multiple species with 53%, 76% and ~100% oral bioavailability in mouse, rat and dog, respectively. CC-115 is tested at lower doses of 0.25, 0.5 and 1 mg/kg bid or 1 mg/kg qd, with observed corresponding tumor volume reductions of 46%, 57%, 66% and 57% respectively. CC-115 sustains inhibition though 24 hours. At the 1 mg/kg dose CC-115 shows significant inhibition at 1 and 3 hours, CC-115 demonstrating inhibition through 10 hours. CC-115 is evaluated using both once (qd) and twice (bid) daily dosing schedules[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	An HTR-FRET substrate phosphorylation assay is employed for mTOR kinase. PI3Kα IC_{50} determinations are outsourced using the mobility shift assay format. Compounds (e.g., CC-115) are assessed against concentrations of ATP at approximately the Km for the assay, with average ATP Km of 15 μM and 50 μM for the mTOR and PI3K assays, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	PC-3 cells are cultured in growth media. For biomarker studies cells are treated for 1 h and then assayed for pS6 and pAkt levels using MesoScale technology. For proliferation experiments, cells are treated with compound (e.g., CC-115) and then allowed to grow for 72 h. All data are normalized and represented as a percentage of the DMSO-treated cells. Results are then expressed as IC_{50} values[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Encouraged by the observed exposures, CC-115 is advanced into single dose PK/PD studies assessing mTOR pathway biomarker inhibition in tumor bearing mice. PC-3 tumor-bearing mice are administered with a single dose of CC-115, dosed orally at either 1 or 10 mg/kg, and plasma and tumor samples are collected at various time points for analysis. Significant inhibition of both mTORC1 (pS6) and mTORC2 (pAktS473) is observed for all compounds and the level of biomarker inhibition correlated to plasma compound levels. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.

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REFERENCES

[1]. Mortensen DS, et al. Optimization of a Series of Triazole Containing Mammalian Target of Rapamycin (mTOR) Kinase Inhibitors and the Discovery of CC-115. J Med Chem. 2015 Jul 23;58(14):5599-5608.

Caution: Product has not been fully validated for medical applications. For research use only.

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