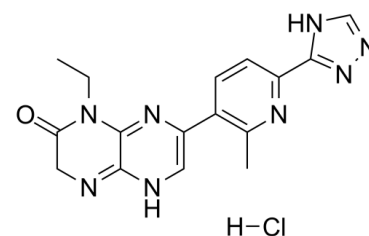


Data Sheet

Product Name:	CC-115 (hydrochloride)
Cat. No.:	CS-5379
CAS No.:	1300118-55-1
Molecular Formula:	C ₁₆ H ₁₇ CIN ₈ O
Molecular Weight:	372.81
Target:	DNA-PK; mTOR
Pathway:	Cell Cycle/DNA Damage; PI3K/Akt/mTOR
Solubility:	DMSO : ≥ 30 mg/mL (80.47 mM)



BIOLOGICAL ACTIVITY:

CC-115 hydrochloride 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: IC_{50} : 21 nM (mTOR), 13 nM (DNA-PK), 852 nM (PI3K α)^[1] mTORC1, mTORC2^[1] **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 μ M, only one kinase other than mTOR kinase is identified with more than 50% inhibition (cFMS 57%, IC_{50} =2.0 μ M). 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- α (IC_{50} =0.85 μ M), ATR (50% inhibition at 30 μ M) and ATM (IC_{50} >30 μ M). The IC_{50} values for CC-115 are >10 μ M against a panel of CYP enzymes and >33 μ M for the hERG (human ether-a-go-go-related gene) ion channel. When screened in a single point assay at 10 μ M against a Cerep receptor and enzyme panel only one target is inhibited >50% (PDE3, IC_{50} =0.63 μ M)^[1]. **In Vivo**: CC-115 hydrochloride 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].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: ^[1]An HTR-FRET substrate phosphorylation assay is employed for mTOR kinase. PI3K α 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 K_m for the assay, with average ATP K_m of 15 μ M and 50 μ M for the mTOR and PI3K assays, respectively^[1].

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].

Animal Administration: CC-115 is prepare in vehicle (CMC-Tween) (Mice)^[1].^[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.

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.

CAIndexNames:

Pyrazino[2,3-b]pyrazin-2(1H)-one, 1-ethyl-3,4-dihydro-7-[2-methyl-6-(1H-1,2,4-triazol-5-yl)-3-pyridinyl]-, hydrochloride (1:x)

SMILES:

[H]Cl.O=C1CN=C2C(N1CC)=NC(C3=C(C)N=C(C4=NN=CN4)C=C3)=CN2

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

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA