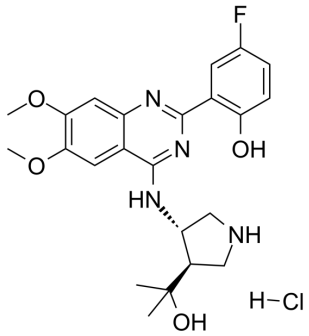
CCT241533 hydrochloride

Cat. No.:	HY-14715B
CAS No.:	1431697-96-9
Molecular Formula:	$C_{23}H_{28}ClFN_4O_4$
Molecular Weight:	478.94
Target:	Checkpoint Kinase (Chk)
Pathway:	Cell Cycle/DNA Damage
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (208.79 mM)

H_2O : 33.33 mg/mL (69.59 mM; Need ultrasonic)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0879 mL	10.4397 mL	20.8794 mL
5 mM	0.4176 mL	2.0879 mL	4.1759 mL
10 mM	0.2088 mL	1.0440 mL	2.0879 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: ≥ 2.5 mg/mL (5.22 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.22 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.22 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (5.22 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.22 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CCT241533 hydrochloride is a potent and selective CHK2 inhibitor with an IC_{50} of 3 nM and a K_i of 1.16 nM[1].

IC_{50} & Target	Chk2 3 nM (IC_{50})	Chk1 245 nM (IC_{50})	Chk2 1.16 nM (Ki)

In Vitro

CCT241533 hydrochloride inhibits CHK2 with an IC_{50} of 3 nM and shows minimal cross reactivity against a panel of kinases at 1 μM. X-ray crystallography confirms that CCT241533 binds to CHK2 in the ATP pocket. CCT241533 blocks CHK2 activity in human tumor cell lines in response to DNA damage, as demonstrated by inhibition of CHK2 autophosphorylation at S516, band-shift mobility changes and HDMX degradation. CCT241533 does not potentiate the cytotoxicity of a selection of genotoxic agents in several cell lines. However, CCT241533 significantly potentiates the cytotoxicity of two structurally distinct PARP inhibitors. Clear induction of the pS516 CHK2 signal is seen with a PARP inhibitor alone and this activation is abolished by CCT241533. The cytotoxicity of CCT241533 in HT-29, HeLa and MCF-7, measured as the growth inhibitory IC_{50} (GI_{50}) by SRB assay, is 1.7, 2.2 and 5.1 μM, respectively[1]. CCT241533 hydrochloride is a potent CHK2 inhibitor (IC_{50}=3 nM), with selectivity (63-fold) over CHK1(IC_{50}=190 nM) and low hERG inhibition (IC_{50}=22 μM)[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]

HT-29, HeLa and MCF-7 cells are exposed to a fixed concentration (GI_{50}) of CCT241533 in combination with increasing concentrations of either PARP inhibitor or cytotoxic drug in a 96 hour SRB assay or 7-10 day colony forming assay. The ability of CCT241533 to enhance cell killing is expressed as a potentiation index (PI) which is the ratio of GI_{50} for the genotoxic or PARP inhibitor alone: GI_{50} for the genotoxic or PARP inhibitor in combination with a CHK2 inhibitor. Thus PI>1 indicates potentiation and PI<1 indicates protection[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Differ. 2021 Jul;28(7):2060-2082.
- J Cell Biol. 2021 Feb 1;220(2):e201911025.
- Int J Mol Sci. 2022, 23(20), 12290.
- J Chem Inf Model. 2017 Nov 27;57(11):2699-2706.

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REFERENCES

[1]. Anderson VE, et al. CCT241533 is a potent and selective inhibitor of CHK2 that potentiates the cytotoxicity of PARP inhibitors. Cancer Res. 2011 Jan 15;71(2):463-72.

[2]. Caldwell JJ, et al. Structure-based design of potent and selective 2-(quinazolin-2-yl)phenol inhibitors of checkpoint kinase 2. J Med Chem. 2011 Jan 27;54(2):580-90.

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