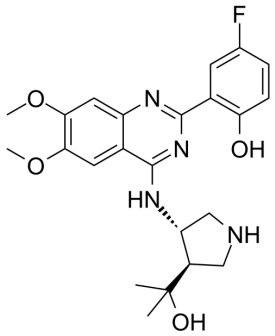
CCT241533

Cat. No.:	HY-14715
CAS No.:	1262849-73-9
Molecular Formula:	$C_{23}H_{27}FN_4O_4$
Molecular Weight:	442.48
Target:	Checkpoint Kinase (Chk)
Pathway:	Cell Cycle/DNA Damage
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	CCT241533 is a potent and selective ATP competitive inhibitor of CHK2 with an IC_{50} of 3 nM and 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.
- 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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