

Product Data Sheet

Product Name: CCT241533 hydrochloride

Cat. No.: GC17105

Chemical Properties

Cas. No. 1431697-96-9

Chemical Name (6Z)-4-fluoro-6-[4-[(3S,4R)-4-(2-hydroxypropan-2-yl)pyrrolidin-3-yl]amino]-6,7-dimethoxy-1H-quinazolin-2-ylidene]cyclohexa-2,4-dien-1-one;hydrochloride

SMILES CC(C)(C1CNCC1NC2=NC(=C3C=C(C=CC3=O)F)NC4=CC(=C(C=C42)OC)OC)O.Cl

Formula $C_{23}H_{28}ClFN_4O_4$ M.Wt 478.94

Solubility DMF: 30 mg/ml, DMSO: 30 mg/ml, Ethanol: 5 mg/ml, PBS (pH 7.2): 500 μ g/ml
Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

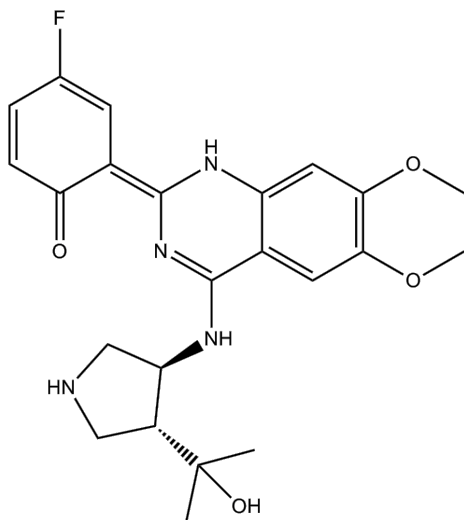
Caution: Product has not been fully validated for medical applications. For research use only.

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Address: 10292 Central Ave. #205, Montclair, CA, USA

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Structure



HCl

Protocol

Cell experiment: HT-29, HeLa and MCF-7 cells are exposed to a fixed concentration (GI50) 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 GI50 for the genotoxic or PARP inhibitor alone: GI50 for the genotoxic or PARP inhibitor in combination with a CHK2 inhibitor. Thus $PI > 1$ indicates potentiation and $PI < 1$ indicates inhibition.

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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.

Background

CHK2 is a checkpoint kinase involved in the ATM-mediated response to double-strand DNA breaks. Inhibitors of CHK2 may increase the efficacy of genotoxic cancer therapies. CCT241533 has been identified and characterized as a novel CHK2 kinase inhibitor.

In vitro: CCT241533 inhibited CHK2 with an IC₅₀ of 3 nmol/L and showed minimal cross-reactivity against a panel of kinases at 1 mmol/L. CCT241533 did not potentiate the cytotoxicity of a selection of genotoxic agents in several cell lines [1]. Moreover, as the most potent CHK2 inhibitor identified in the series, CCT241533 showed potent selectivity (63-fold) over CHK1 and low hERG inhibition [2].

In silico: X-ray crystallography confirmed that CCT241533 bound to CHK2 in the ATP pocket. Overall, the binding mode was found to be very highly conserved relative to previous compounds, with all of the key hydrogen bond interactions maintained. The potency gained with CCT241533 therefore appeared to be due to the presence of the two methoxy substituents occupying the solvent exposed region of the enzyme, and contributions from the isopropyl alcohol substituent [2].

Clinical trial: No clinical data are available currently

References:

- [1] Anderson VE, Walton MI, Eve PD, Boxall KJ, Antoni L, Caldwell JJ, Aherne W, Pearl LH, Oliver AW, Collins I, Garrett MD. CCT241533 is a potent and selective inhibitor of CHK2 that potentiates the cytotoxicity of PARP inhibitors. *Cancer Res.* 2011;71(2):463-72.
- [2] Caldwell JJ, Welsh EJ, Matijssen C, Anderson VE, Antoni L, Boxall K, Urban F, Hayes A, Raynaud FI, Rigoreau LJ, Raynham T, Aherne GW, Pearl LH, Oliver AW, Garrett MD, Collins I. Structure-based design of potent and selective 2-(quinazolin-2-yl)phenol inhibitors of checkpoint kinase 2. *J Med Chem.* 2011;54(2):580-90.

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