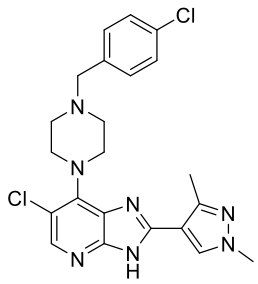
Product data sheet

MedKoo Cat#: 407950 Name: CCT241736 CAS#: 1402709-93-6 Chemical Formula: $C_{22}H_{23}Cl_2N_7$ Exact Mass: 455.1392 Molecular Weight: 456.375	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
CCT241736 is a potent and orally active and dual FLT3-Aurora inhibitor. CCT241736 has IC50 values against FLT3, Aurora A and Aurora B of 0.035, 0.015 and 0.1 μM respectively. CCT241736 inhibits a wide range of FLT3 mutants, including FLT3-ITD, -D835Y, -D835H, -K663Q and -N841I. In cellular assays, CCT241736 inhibits viability of the human FLT3-ITD positive AML cell lines MOLM-13 and MV-4;11 with EC50 values of 0.1 and 0.27

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	75	164.34

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.19 mL	10.96 mL	21.91 mL
5 mM	0.44 mL	2.19 mL	4.38 mL
10 mM	0.22 mL	1.10 mL	2.19 mL
50 mM	0.04 mL	0.22 mL	0.44 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Bavetsias V, Crumpler S, Sun C, Avery S, Atrash B, Faisal A, Moore AS, Kosmopoulou M, Brown N, Sheldrake PW, Bush K, Henley A, Box G, Valenti M, de Haven Brandon A, Raynaud FI, Workman P, Eccles SA, Bayliss R, Linardopoulos S, Blagg J. Optimization of imidazo[4,5-b]pyridine-based kinase inhibitors: identification of a dual FLT3/Aurora kinase inhibitor as an orally bioavailable preclinical development candidate for the treatment of acute myeloid leukemia. J Med Chem. 2012 Oct 25;55(20):8721-34. doi: 10.1021/jm300952s. Epub 2012 Oct 8. PMID: 23043539; PMCID: PMC3483018.

2. Wood FL, Shepherd S, Hayes A, Liu M, Grira K, Mok Y, Atrash B, Faisal A, Bavetsias V, Linardopoulos S, Blagg J, Raynaud FI. Metabolism of the dual FLT-3/Aurora kinase inhibitor CCT241736 in preclinical and human in vitro models: Implication for the choice of toxicology species. Eur J Pharm Sci. 2019 Nov 1;139:104899. doi: 10.1016/j.ejps.2019.04.004. Epub 2019 Apr 3. PMID: 30953752; PMCID: PMC6892276.

In vivo study

1. Bavetsias V, Crumpler S, Sun C, Avery S, Atrash B, Faisal A, Moore AS, Kosmopoulou M, Brown N, Sheldrake PW, Bush K, Henley A, Box G, Valenti M, de Haven Brandon A, Raynaud FI, Workman P, Eccles SA, Bayliss R, Linardopoulos S, Blagg J. Optimization of imidazo[4,5-b]pyridine-based kinase inhibitors: identification of a dual FLT3/Aurora kinase inhibitor as an orally

bioavailable preclinical development candidate for the treatment of acute myeloid leukemia. J Med Chem. 2012 Oct 25;55(20):8721-34. doi: 10.1021/jm300952s. Epub 2012 Oct 8. PMID: 23043539; PMCID: PMC3483018.

2. Moore AS, Faisal A, Mak GWY, Miraki-Moud F, Bavetsias V, Valenti M, Box G, Hallsworth A, de Haven Brandon A, Xavier CPR, Stronge R, Pearson ADJ, Blagg J, Raynaud FI, Chopra R, Eccles SA, Taussig DC, Linardopoulos S. Quizartinib-resistant FLT3-ITD acute myeloid leukemia cells are sensitive to the FLT3-Aurora kinase inhibitor CCT241736. Blood Adv. 2020 Apr 14;4(7):1478-1491. doi: 10.1182/bloodadvances.2019000986. PMID: 32282883; PMCID: PMC7160287.

7. Bioactivity

Biological target:

CCT241736 is a potent and orally bioavailable dual FLT3 and Aurora kinase inhibitor, which inhibits Aurora kinases (Aurora-A Kd, 7.5 nM, IC50, 38 nM; Aurora-B Kd, 48 nM), FLT3 kinase (Kd, 6.2 nM), and FLT3 mutants including FLT3-ITD (Kd, 38 nM) and FLT3(D835Y) (Kd, 14 nM).

In vitro activity

CCT241736 (Compound 27e) is a potent and orally bioavailable dual FLT3 and Aurora kinase inhibitor, which inhibits Aurora kinases (Aurora-A Kd, 7.5 nM, IC50, 38 nM, Aurora-B Kd, 48 nM), FLT3 kinase (Kd, 6.2 nM), and FLT3 mutants including FLT3-ITD (Kd, 38 nM) and FLT3(D835Y) (Kd, 14 nM). CCT241736 exhibits antiproliferative activity in a range of human tumor cell lines, such as HCT116 human colon carcinoma (GI50, 0.300 μM), the human FLT3-ITD positive AML cell lines MOLM-13 (GI50, 0.104 μM) and MV4-11 (GI50, 0.291 μM). CCT241736 also inhibits both the autophosphorylation of Aurora-A at T288 (a biomarker for Aurora-A inhibition: IC50, 0.030 μM) and histone H3 phosphorylation at S10 (a biomarker for Aurora-B inhibition: IC50, 0.148 μM), consistent with potent cellular activity versus both Aurora-A and -B. CCT241736 suppresses Aurora-A in MOLM-13 cells with concomitant inhibition of FLT3 signaling.

Reference: J Med Chem. 2012 Oct 25;55(20):8721-34. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23043539/

In vivo activity

Human tumor xenograft experiments (MOLM-13) were carried out in athymic mice to evaluate the efficacy of CCT241736 in vivo. CCT241736 reduced tumor growth compared with that in vehicle-treated mice in a dose-dependent manner with no observed toxicity on chronic dosing (Figure 3A). To analyze the PD activity of CCT241736 in vivo, tumors were collected at 2 hours after the final dose, and the lysates were analyzed by immunoblotting. Reduction of phospho-Aurora-A and phospho-STAT5 indicates inhibition of both Aurora A and FLT3 in a dose-dependent manner (Figure 3B). Similarly, survivin levels were reduced in a dose-dependent manner, which indicates that CCT241736 induced apoptosis in vivo. A confirmatory study in a second in vivo FLT3-ITD+ AML human tumor xenograft model (MV4-11) showed that CCT241736 significantly inhibits the growth of MV4-11 xenografts with clear inhibition of both HH3 and STAT5 phosphorylation at 2 hours after the final dose, indicating a dual inhibition of both Aurora and FLT3 downstream pathways in the tumor.15 To demonstrate that Aurora kinase inhibition by CCT241736 makes a significant contribution to efficacy in FLT3-mutated AML, samples of the MV4-11 tumors from the animals dosed with 100 mg/kg at 2 hours after administration were analyzed by immunofluorescence microscopy. More than one third (36%) of mitotic cells from tumors treated with CCT241736 formed monopolar or abnormal spindles, a typical phenotype for Aurora kinase inhibition.23 In comparison, this phenotype was observed in only 4% of mitotic cells in tumors from mice treated with vehicle control (Figure 3C-D). These data confirm the contribution of Aurora inhibition by CCT241736 to the in vivo efficacy and the already known induced phenotype from previous studies using Aurora inhibitors.

Reference: Blood Adv. 2020 Apr 14;4(7):1478-1491. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32282883/