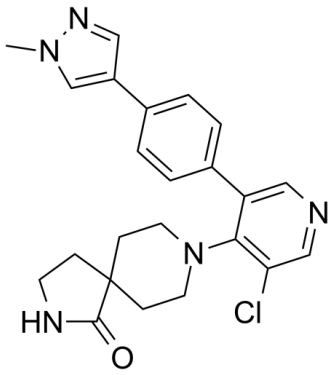
Data Sheet

Product Name:	CCT251545
Cat. No.:	CS-5359
CAS No.:	1661839-45-7
Molecular Formula:	C23H24ClN5O
Molecular Weight:	421.92
Target:	Wnt
Pathway:	Stem Cell/Wnt
Solubility:	DMSO : ≥ 50 mg/mL (118.51 mM)



BIOLOGICAL ACTIVITY:

CCT251545 is an orally bioavailable and potent inhibitor of **WNT** signaling with an **IC_{50}** of 5 nM in 7dF3 cells[1]. IC50 & Target: IC50: 5 nM (WNT, 7dF3 cells)[1] **In Vitro:** CCT251545 potently inhibits WNT pathway activity in COLO205-F1756 clone 4 (an APC -mutant human colorectal cancer cell line engineered to express a modified luciferase-based WNT reporter construct) with an IC_{50} of 0.035 μM [1].

CCT251545 has weak inhibition of tankyrase enzymes (TNKS1 IC_{50} > 10 μM, TNKS2 IC_{50} = 15.0)[1].

CCT251545 is a potent and selective chemical probe for the human mediator complex-associated protein kinases CDK8 and CDK19 with >100-fold selectivity over 291 other kinases[2].

CCT251545 alters WNT pathway-regulated gene expression and other on-target effects of modulating CDK8 and CDK19, including expression of genes regulated by STAT1[2].

CCT251545 also reduces phospho-$STAT1^{SER727}$ levels in SW620 cells with an IC_{50} of 9 nM[2].

CCT251545 displays potent cell-based activity[2].

In Vivo: CCT251545 (70mg/kg; p.o.; twice daily) causes an inhibition of tumor growth in NCr athymic mice bearing established SW620 human colorectal cancer xenografts[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] SW620 cells were incubated for 2 h with indicated concentrations (30, 3, 0.3, 0.03 and 0.003 μM) of CCT251545. Control cells were treated with 0.3% DMSO. Cells were lysed in lysis buffer (50 mM Tris-HCl pH 7.4, 150 mM NaCl, 1% Triton X-100, 1 mM EDTA, 20 mM β-Glycerolphosphate, 1% Phosphatase-Inhibitor Cocktail Set II, 0.1% Protease-Inhibitor Cocktail Set III, 0.01% Benzonase and each lysate was split into two aliquots. One aliquot was kept at 4°C and the other aliquot was heated at 50°C for 3 min followed by cooling at room temperature for 3 min. After centrifugation (4°C, 16,000 × g, 20 min) CDK8 and CDK19 levels were determined in supernatants using a bead-based ELISA. Animal administration [1] To assess the in vivo activity of CCT251545, we developed an animal model of intestinal hyperplasia dependent upon the expression of a dox-inducible mutant β-catenin transgene. Oral dosing of CCT251545 for 2 d (75, 37.5 and 18.75 mg/kg twice a day) dose-dependently reduced the length of hyperplastic crypts, with the maximum effect similar to that of the removal of dox. We observed a concomitant reduction in proliferation and increased cell differentiation in goblet cells, as quantified by BrdU and Alcian Blue staining, respectively.

References:

[1]. Mallinger A, et al. Discovery of potent, orally bioavailable, small-molecule inhibitors of WNT signaling from a cell-based pathway screen. J Med Chem. 2015 Feb 26;58(4):1717-35.

[2]. Dale T, et al. A selective chemical probe for exploring the role of CDK8 and CDK19 in human disease. Nat Chem Biol. 2015 Dec;11(12):973-980.

CAIndexNames:

2,8-Diazaspiro[4.5]decan-1-one, 8-[3-chloro-5-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]-4-pyridinyl]-

SMILES:

O=C1NCCC12CCN(C3=C(Cl)C=NC=C3C4=CC=C(C5=CN(C)N=C5)C=C4)CC2

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