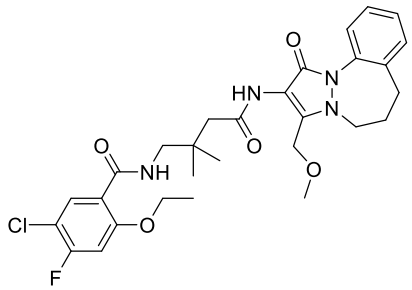
Product data sheet

MedKoo Cat#: 565585 Name: CB-6644 CAS#: 2316817-88-4 Chemical Formula: $C_{29}H_{34}ClFN_4O_5$ Exact Mass: 572.2202 Molecular Weight: 573.0624	
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:
CB-6644 is a novel allosteric selective inhibitor of the ruvbl1/2 complex with anti-cancer activity. CB-6644 blocks the ATPase activity of RUVBL1/2 with an IC50 of 15 nM. CB-6644 interacts specifically with RUVBL1/2 in cancer cells, leading to cell death. Importantly, drug-acquired-resistant cell clones have amino acid mutations in either RUVBL1 or RUVBL2, suggesting that cell killing is an on-target consequence of RUVBL1/2 engagement. In xenograft models of acute myeloid leukemia and multiple myeloma, CB-6644 significantly reduced tumor growth without obvious toxicity.

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	100.0	174.5

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.75 mL	8.73 mL	17.45 mL
5 mM	0.35 mL	1.75 mL	3.49 mL
10 mM	0.17 mL	0.87 mL	1.75 mL
50 mM	0.03 mL	0.17 mL	0.35 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. Assimon VA, Tang Y, Vargas JD, Lee GJ, Wu ZY, Lou K, Yao B, Menon MK, Pios A, Perez KC, Madriaga A, Buchowiecki PK, Rolfe M, Shawver L, Jiao X, Le Moigne R, Zhou HJ, Anderson DJ. CB-6644 Is a Selective Inhibitor of the RUVBL1/2 Complex with Anticancer Activity. ACS Chem Biol. 2019 Feb 15;14(2):236-244. doi: 10.1021/acschembio.8b00904. Epub 2019 Jan 25. PMID: 30640450.

In vivo study

1. Assimon VA, Tang Y, Vargas JD, Lee GJ, Wu ZY, Lou K, Yao B, Menon MK, Pios A, Perez KC, Madriaga A, Buchowiecki PK, Rolfe M, Shawver L, Jiao X, Le Moigne R, Zhou HJ, Anderson DJ. CB-6644 Is a Selective Inhibitor of the RUVBL1/2 Complex with Anticancer Activity. ACS Chem Biol. 2019 Feb 15;14(2):236-244. doi: 10.1021/acschembio.8b00904. Epub 2019 Jan 25. PMID: 30640450.

7. Bioactivity
Biological target:

Product data sheet

CB-6644 is a selective inhibitor of RUVBL1/2 complex with anti-cancer activity and blocks the ATPase activity of RUVBL1/2 with an IC50 of 15 nM.

In vitro activity

CB-6644 was analyzed to determine whether it could target the RUVBL1/2 complex in cells. A cellular thermal shift assay (CETSA) was developed to assess target engagement by measuring the thermal stabilization of a protein upon ligand binding. The apparent melting curves for RUVBL1 and RUVBL2 were determined. At 65 °C, the majority of RUVBL1 and RUVBL2 was denatured and precipitated in the DMSO control but not in the sample treated with CB-6644 (Figure S4a). These results suggest that CB-6644 binds to and stabilizes RUVBL1/2 in cells. Next, the sensitivity of this interaction was determined. In an isothermal dose–response fingerprint (IDRF) CETSA experiment, the amounts of stabilized soluble RUVBL1, RUVBL2, and p97 were quantified in the presence of increasing concentrations of CB-6644. Consistent with our specificity studies, CB-6644 did not stabilize p97, another AAA ATPase family member. However, dose-dependent stabilization of both RUVBL1 and RUVBL2 with half-maximal thermal stabilization concentrations of ~350 nM (Figure 4a) was observed. Together, these results illustrate that CB-6644 directly and potently engages with RUVBL1/2 in cells.

Reference: ACS Chem Biol. 2019 Feb 15;14(2):236-244. https://doi.org/10.1021/acschembio.8b00904

In vivo activity

The antitumor activity of the compound in xenograft tumor models was assessed. First, the pharmacokinetic (PK) properties of the compound were evaluated. Following a single dose of CB-6644, the concentration of the compound in plasma was determined at various time points, and the oral bioavailability (%F) was found to be 35.9% (Figure 7a). This datum demonstrates that CB-6644 is orally bioavailable and p.o. administration gives a sufficient drug exposure level to study antitumor effects. The antitumor activity of CB-6644 was assessed in SCID-beige mice bearing human tumor xenografts derived from either Burkitt's lymphoma (Ramos) or multiple myeloma (RPMI8226) cell lines that were among the most sensitive to CB-6644 treatment in our cell panel screen (Figure 4b). CB-6644 was administered by oral gavage once (QD) or twice (BID) daily, and tumor growth inhibition (TGI) was calculated on the last day of treatment (Figure 7b,c). This dosing schedule was well-tolerated in tumor-bearing mice, with less than 5% body weight loss throughout the studies (Figure S6). Both regimens showed antitumor activity in Ramos and RPMI8226, with the BID dosing regimen showing greater efficacy than the QD schedule (TGI of 68 and 81% in Ramos and RPMI8226, respectively). These data provide the strongest validation to date of RUVBL1/2 as a promising therapeutic cancer target.

Reference: ACS Chem Biol. 2019 Feb 15;14(2):236-244. https://doi.org/10.1021/acschembio.8b00904