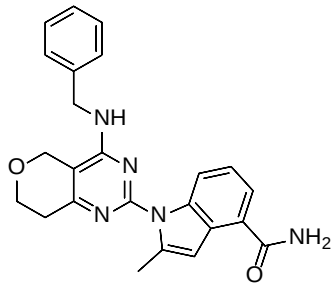
Product data sheet

MedKoo Cat#: 206489 Name: CB-5083 CAS#: 1542705-92-9 Chemical Formula: $C_{24}H_{23}N_5O_2$ Exact Mass: 413.1852 Molecular Weight: 413.40	
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-5083 is a novel first in class, potent orally bio-available p97 inhibitor that disrupts cellular protein homeostasis and demonstrates anti-tumor activity in solid and hematological models . CB-5083 causes rapid and sustained accumulation of poly-ubiquitin in tumor xenografts after a single administration. CB-5083 showed activity to inhibit tumor growth in multiple rodent models of human cancer. Furthermore, CB-5083 appears to exhibit greater potency over current proteasome inhibitors that further validate targeting p97 and protein homeostasis in the treatment of cancer.

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	91.0	220.13
Ethanol	29.0	70.15

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.42 mL	12.09 mL	24.19 mL
5 mM	0.48 mL	2.42 mL	4.84 mL
10 mM	0.24 mL	1.21 mL	2.42 mL
50 mM	0.05 mL	0.24 mL	0.48 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. Gareau A, Rico C, Boerboom D, Nadeau ME. In vitro efficacy of a first-generation valosin-containing protein inhibitor (CB-5083) against canine lymphoma. Vet Comp Oncol. 2018 Sep;16(3):311-317. doi: 10.1111/vco.12380. Epub 2018 Jan 4. PMID: 29314493.

In vivo study

1. Le Moigne R, Aftab BT, Djakovic S, Dhimolea E, Valle E, Murnane M, King EM, Soriano F, Menon MK, Wu ZY, Wong ST, Lee GJ, Yao B, Wiita AP, Lam C, Rice J, Wang J, Chesi M, Bergsagel PL, Kraus M, Driessen C, Kiss von Soly S, Yakes FM, Wustrow D, Shawver L, Zhou HJ, Martin TG 3rd, Wolf JL, Mitsiades CS, Anderson DJ, Rolfe M. The p97 Inhibitor CB-5083 Is a Unique Disrupter of Protein Homeostasis in Models of Multiple Myeloma. Mol Cancer Ther. 2017 Nov;16(11):2375-2386. doi: 10.1158/1535-7163.MCT-17-0233. Epub 2017 Sep 6. PMID: 28878026.

7. Bioactivity
Biological target: CB-5083 selectively inhibits p97 through its D2 site with the IC50 of 11 nM.

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In vitro activity

p97 inhibition with small molecules has been shown to induce endoplasmic reticulum (ER) stress and activate the unfolded protein response (UPR). CB-5083 caused a strong induction of the UPR as measured by the phosphorylation of PERK and accumulation of sXBP1 and BiP (Fig. 2A; Supplementary Fig. S2). CB-5083 treatment led to a robust induction of the transcription factor CCAAT/enhancer-binding protein homologous protein (CHOP). K48-linked polyubiquitin accumulation, a hallmark of inhibition of protein degradation, was followed as a pathway marker for p97 inhibition (Fig. 2A and B). CB-5083, like bortezomib, induced a rapid accumulation of K48-linked polyubiquitinated proteins in cultured cells. The UPR was activated, and CHOP protein expression increased up to 2.7-fold compared with baseline levels. Consequently, apoptosis was activated, as demonstrated by an increase in cleaved PARP (cPARP) levels (Fig. 2C).

Reference: Mol Cancer Ther. 2017 Nov;16(11):2375-2386. https://mct.aacrjournals.org/content/16/11/2375.long

In vivo activity

The P97 inhibitor CB-5083 can inhibit osteosarcoma cell proliferation and effectively induce apoptosis. The in vivo antitumor ability of the P97 inhibitor CB-5083 was investigated using a nude mouse xenograft model established with SJSA-1 cells. Once the tumor volume reached approximately 100 mm3, the mice were randomly divided into two groups (vehicle group and CB-5083 group): the CB-5083 group was treated with 100 mg/kg CB-5083 every day, whereas the vehicle group was treated with normal saline (with the same volume of DMSO). The P97 inhibitor CB-5083 inhibited tumor growth beginning 15 days after the first injection, and significant inhibition was detected through the end of the study (Figure 3A). The average tumor weight of the vehicle group was 823 mg, whereas that of the CB-5083 group was 416 mg, which also indicated an in vivo reduction in osteosarcoma growth (Figure 3B). The average body weights of the nude mice in the different groups showed no significant changes, which indicated that CB-5083 exhibits low toxicity (Figure 3C). These results demonstrated that the P97 inhibitor CB-5083 exhibits prominent antitumor properties and no distinct toxicity in vivo.

Reference: Am J Transl Res. 2020 Jun 15;12(6):2956-2967. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7344079/