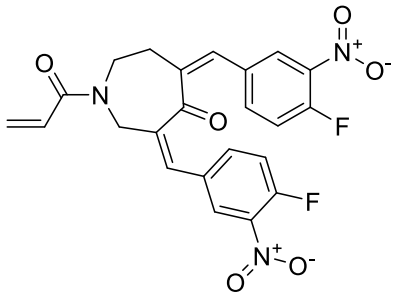
Product data sheet

MedKoo Cat#: 206324 Name: VLX1570 CAS#: 1431280-51-1 Chemical Formula: $C_{23}H_{17}F_2N_3O_6$ Exact Mass: 469.1085 Molecular Weight: 469.4008	
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:

VLX1570 is an inhibitor of the 19S proteasome-specific deubiquitylating enzymes (DUBs) USP14 and UCHL5, with apoptosis-inducing and antineoplastic activities. Upon administration, VLX1570 specifically binds to both USP14 and UCHL5, thereby blocking their deubiquitylating activity. This blocks the ubiquitin proteasome degradation pathway, prevents the degradation of defective proteins, and leads to an accumulation of poly-ubiquitylated proteins. This induces the unfolded protein response (UPR) and results in both the induction of tumor cell apoptosis and the inhibition of tumor cell growth.

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
DMF	25.0	53.26
DMF:PBS (pH 7.2) (1:2)	0.3	0.64
DMSO	47.0	100.13

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.13 mL	10.65 mL	21.30 mL
5 mM	0.43 mL	2.13 mL	4.26 mL
10 mM	0.21 mL	1.07 mL	2.13 mL
50 mM	0.04 mL	0.21 mL	0.43 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. Pellegrini P, Selvaraju K, Faustini E, Mofers A, Zhang X, Ternerot J, Schubert A, Linder S, D Arcy P. Induction of ER Stress in Acute Lymphoblastic Leukemia Cells by the Deubiquitinase Inhibitor VLX1570. Int J Mol Sci. 2020 Jul 4;21(13):4757. doi: 10.3390/ijms21134757. PMID: 32635430; PMCID: PMC7369842.
2. Mazurkiewicz M, Hillert EK, Wang X, Pellegrini P, Olofsson MH, Selvaraju K, D'Arcy P, Linder S. Acute lymphoblastic leukemia cells are sensitive to disturbances in protein homeostasis induced by proteasome deubiquitinase inhibition. Oncotarget. 2017 Mar 28;8(13):21115-21127. doi: 10.18632/oncotarget.15501. PMID: 28423502; PMCID: PMC5400570.

In vivo study

1. Shukla N, Somwar R, Smith RS, Ambati S, Munoz S, Merchant M, D'Arcy P, Wang X, Kobos R, Antczak C, Bhinder B, Shum D, Radu C, Yang G, Taylor BS, Ng CK, Weigelt B, Khodos I, de Stanchina E, Reis-Filho JS, Ouerfelli O, Linder S, Djaballah H, Ladanyi M. Proteasome Addiction Defined in Ewing Sarcoma Is Effectively Targeted by a Novel Class of 19S Proteasome Inhibitors.

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Cancer Res. 2016 Aug 1;76(15):4525-34. doi: 10.1158/0008-5472.CAN-16-1040. Epub 2016 Jun 2. PMID: 27256563; PMCID: PMC5484002.

7. Bioactivity

Biological target:

VLX1570 is a competitive inhibitor of proteasome deubiquitinases (DUBs) with an IC50 of approximate 10 μM.

In vitro activity

Inhibition of proteasome ubiquitin processing following VLX1570 treatment results in the accumulation of high molecular weight polyubiquitinated substrates in cells. A dose-dependent increase in high-molecular polyubiquitinated proteins in ALL cells following exposure to VLX1570 (Figure 1B) was found. The increases in polyubiquitinated proteins occurred at drug concentrations that reduced the number of viable cells (50 – 100 nM), consistent with the notion that the growth inhibitory effect of the drug is due to UPS inhibition. The extent of accumulation of misfolded protein substrates in VLX1570-exposed cells was previously found to be associated with cytotoxicity. In general cells with high protein turnover rates respond to decreased UPS flux via the induction of chaperones to counteract the accumulation of misfolded proteins. VLX1570 increased the expression of the inducible form of Hsp70 (HSP70B´) in all ALL cell lines tested (Figure 1B). Induction of HSP70B´ was generally observed at drug concentrations that induced the accumulation of polyubiquitin.

Reference: Oncotarget. 2017 Mar 28; 8(13): 21115–21127. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5400570/

In vivo activity

To evaluate the in vivo activity of benzyl-4-piperidone compounds, a GFP-luciferase expressing A673 xenograft model was treated with b-AP15 following injection of cells to study the effect on tumor formation. Treatment with b-AP15 resulted in undetectable tumors by imaging at 4 weeks (Fig S3A). Next, bortezomib and b-AP15 were compared in an A673 xenograft model and demonstrated superior growth inhibition and improved survival with the former (Fig S3B and S3C). The ability of b-AP15 and VLX1570 to inhibit the growth of two EWS cell line xenografts, A673 and TC-71, was tested. Athymic mice were treated with b-AP15 (25mg/kg), VLX1570 (4.4mg/kg), or vehicle daily via intraperitoneal administration. Growth of A673 and TC-71 xenograft tumors was significantly reduced by both compounds with VLX1570 being more potent (Fig. 3C).

Reference: Cancer Res. 2016 Aug 1; 76(15): 4525–4534. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5484002/