Carfilzomib (PR-171)

Print

Technical Data

Molecular Weight	719.91	**Storage**	3 years	-20°C	powder
Formula	$C_{40}H_{57}N_5O_7$		2 years	-80°C	in solvent
CAS No.	868540-17-4	**Synonyms**	N/A		
Solubility (25°C) *	In vitro	DMSO	50 mg/mL (69.45 mM)		
		Water	<1 mg/mL		
		Ethanol	<1 mg/mL		
	In vivo	2% DMSO+castor oil	10mg/mL		

* <1 mg/ml means slightly soluble or insoluble.
* Please note that Selleck tests the solubility of all compounds in-house, and the actual solubility may differ slightly from published values. This is normal and is due to slight batch-to-batch variations.

Chemical Name	L-Phenylalaninamide, (αS)-α-[[2-(4-morpholinyl)acetyl]amino]benzenebutanoyl-L-leucyl-N-[(1S)-3-methyl-1-[[(2R)-2-methyl-2-oxiranyl]carbonyl]butyl]-

Preparing Stock Solutions

Volume (DMSO) / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.3891 mL	6.9453 mL	13.8906 mL
5 mM	0.2778 mL	1.3891 mL	2.7781 mL
10 mM	0.1389 mL	0.6945 mL	1.3891 mL
50 mM	0.0278 mL	0.1389 mL	0.2778 mL

Biological Activity

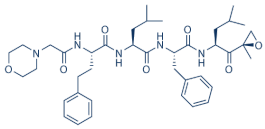
Description	Carfilzomib (PR-171) is an irreversible **proteasome** inhibitor with **IC50** of <5 nM in ANBL-6 cells, displayed preferential in vitro inhibitory potency against the ChT-L activity in the β5 subunit, but little or no effect on the PGPH and T-L activities.
Targets	Proteasome [1] (ANBL-6 cells) 5 nM
In vitro	Carfilzomib inhibits proliferation in a variety of cell lines and patient-derived neoplastic cells, including multiple myeloma, and induced intrinsic and extrinsic apoptotic signaling pathways and activation of c-Jun-N-terminal kinase (JNK). Carfilzomib reveals enhanced anti-MM activity compared with bortezomib, overcome resistance to bortezomib and other agents, and acts synergistically with dexamethasone (Dex). Carfilzomib shoes preferential in vitro inhibitory potency against the ChT-L activity in the β5 subunit, with over 80% inhibition at doses of 10 nM. Short exposure to low-dose Carfilzomib leads to preferential binding specificity for the β5 constitutive 20S proteasome and the β5i immunoproteasome subunits. Measurement of caspase activity in ANBL-6 cells pulsed with Carfilzomib reveals substantial increases in caspase-8, caspase-9, and caspase-3 activity after 8 hours, giving a 3.2-, 3.9- and 6.9-fold increase, respectively, over control cells after 8 hours. In carfilzomib pulse-treated cells, the mitochondrial membrane integrity is decreased to 41% (Q1 + Q2), compared with 75% in vehicle-treated control cells. [1] In another study, Carfilzomib has also shown preclinical effectiveness against hematological and solid malignancies. [2] Carfilzomib directly inhibits osteoclasts formation and bone resorption. [3]
In vivo	Carfilzomib moderately reduces tumor growth in an in vivo xenograft model. Carfilzomib effectively decreases multiple myeloma cell viability following continual or transient treatment mimicking. Carfilzomib increases trabecular bone volume, decreases bone resorption and enhances bone formation in non-tumor bearing mice. [3]
Features	

Protocol *(Only for Reference)*

Kinase Assay: [1]

Enzyme-linked immunosorbent assay for subunit profiling of carfilzomib	ANBL-6 cells (2 × 10^6/well) are plated in 96-well plates and treated with Carfilzomib doses from 0.001 to 10 μM for 1 hour. Cells are then lysed (20 mM Tris-HCl, 0.5 mM EDTA), and cleared lysates are transferred to polymerase chain reaction (PCR) plates. A standard curve is generated using untreated ANBL-6 cell lysates starting at a concentration of 6 μg protein/μL. The active site probe [biotin-(CH2)4-Leu-Leu-Leu-epoxyketone; 20 μM] is added and incubated at room temperature for 1 hour. Cell lysates are then denatured by adding 1% sodium dodecyl sulfate (SDS) and heating to 100°C, followed by mixing with 20 μL per well streptavidin-sepharose high-performance beads in a 96-well multiscreen DV plate and incubated for 1 hour. These beads are then washed with enzyme-linked immunosorbent assay (ELISA) buffer (PBS, 1% bovine serum albumin, and 0.1% Tween-20), and incubated overnight at 4°C on a plate shaker with antibodies to proteasome subunits. Antibodies used included mouse monoclonal anti-β1, anti-β2, anti-β1i, and anti-β5i, goat polyclonal anti-β2i, and rabbit

Chemical Structure



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	polyclonal anti-β5 (affinity-purified antiserum against KLH-CWIRVSSDNVADLHDKYS peptide). The beads are washed and incubated for 2 hours with horseradish peroxidase-conjugated secondary goat antirabbit, goat antimouse or rabbit antigoat antibodies. After washing, the beads are developed using the supersignal ELISA picochemiluminescence substrate. Luminescent detection is performed. Raw luminescence is converted to µg/mL by comparison with the standard curve and expressed as the % inhibition relative to vehicle control. Curve fits are generated using the following nonsigmoidal dose-response equation: Y = Bottom + (Top-Bottom)/(1 + 10^((LogEC50 − X) × HillSlope)), where X is the logarithm of concentration, Y is the % inhibition, and EC50 is the dose showing 50% effect.

Cell Assay: [1]

Cell lines	WST-1, ANBL-6 cells
Concentrations	100 nM
Incubation Time	1 hour
Method	WST-1 is used to determine the effects of proteasome inhibitor Carfilzomib on cell proliferation. The inhibition of proliferation is calculated in relation to parallel control cells that receives vehicle alone. A linear spline function is used to interpolate the median inhibitory concentration (IC50) using XLfit 4 software. The degree of resistance (DOR) is calculated using the formula: DOR = IC50(resistant cells)/IC50(sensitive cells). ANBL-6 cells pulsed with 100 nM carfilzomib are washed and suspended in PBS containing 5 µg/mL of JC-1, which exhibits potential-dependent accumulation in mitochondria. Analysis of the mitochondrial membrane potential-dependent color shift from 525 to 590 nm is carried out on a FacScan, and the data are analyzed with CellQuest software.

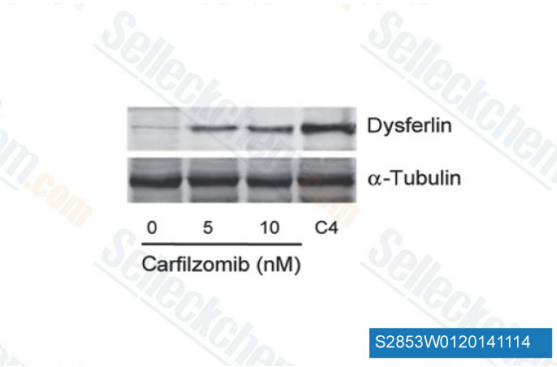
Animal Study: [4]

Animal Models	Beige-nude-XID mice
Formulation	10% sulfobutylether β-cyclodextrin in 10 mmol/L citrate buffer pH 3.5,
Dosages	2.0 mg/kg
Administration	i.v.

References

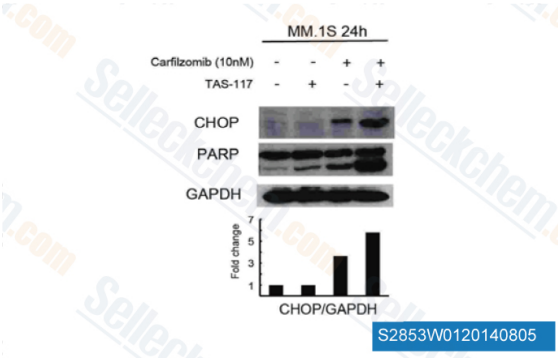
[1] Kuhn DJ, et al. Blood. 2007, 110(9), 3281-3290.
[2] Kuhn DJ, et al. Curr Cancer Drug Targets. 2011, 11(3), 285-295.
[3] Hurchla MA, et al. Leukemia. 2012.
[4] Dasmahapatra G, et al. Mol Cancer Ther. 2011, 10(9), 1686-1697.

Customer Product Validation



Data from [Data independently produced by **Sci Transl Med**, 2014, 6(250), 250ra112]

Validation of activity and specificity of chemical inhibitors of; ATM, ATR, and DNAPK. H460 cells were treated with 1 uM camptothecin (CPT) or 20 ug/ml bleomycin for 1 h in the presence of the indicated inhibitors: DNAPK-i1—NU7026, DNAPK-i2—NU7441. MSH6,



Data from [**Cancer Res**, 2014, 74(16), 4458-69]

MM.1S cells were treated with or without carfilzomib (10 nM) in the presence or absence of TAS-117 (0.5 uM) for 24 h. Whole cell lysates were subjected to western blotting using CHOP, PARP, and GAPDH Abs.The graph represents fold changes of CHOP density relative to GAPDH.

Carfilzomib (PR-171) has been referenced in 16 publications.

Functionally defined therapeutic targets in diffuse intrinsic pontine glioma. [Grasso CS, et al. Nat Med, 2015, 10.1038/nm.3855] PubMed: 25939062

Proteasome inhibitors increase missense mutated dysferlin in patients with muscular dystrophy [Azakir BA, et al Sci Transl Med, 2014, 6(250):250ra112] PubMed: 25143362

GP130 activation induces myeloma and collaborates with MYC. [Dechow T, et al. J Clin Invest, 2014, 124(12):5263-74] PubMed: 25384216

C1013G/CXCR4 acts as a driver mutation of tumor progression and modulator of drug resistance in lymphoplasmacytic lymphoma. [Roccaro AM Blood, 2014, 123(26):4120-31] PubMed: 24711662

Selective and potent akt inhibition triggers anti-myeloma activities and enhances fatal endoplasmic reticulum stress induced by proteasome inhibition [Mimura N,et al. Cancer Res, 2014, 74(16):4458-69] PubMed: 24934808

A Mass Spectrometry Platform for a Streamlined Investigation of Proteasome Integrity, Posttranslational Modifications, and Inhibitor Binding. [Gersch M, et al. Chem Biol, 2015, 10.1016/j.chembiol.2015.01.004] PubMed: 25728267

Reconstructing the temporal progression of HIV-1 immune response pathways [Jain S, et al. Bioinformatics, 2016, 32(12):i253-i261] PubMed: 27307624

Targeting Mcl-1 for multiple myeloma (MM) therapy: Drug-induced generation of Mcl-1 fragment Mcl-1128–350 triggers MM cell death via c-Jun upregulation [Fan F, et al. Cancer Lett, 2014, 343(2):286-94] PubMed: 24120758

Chemotherapy stimulates syndecan-1 shedding: A potentially negative effect of treatment that may promote tumor relapse. [Ramani VC, et al. Matrix Biol, 2014, 35:215-22] PubMed: 24145151

Nrf2- and ATF4-Dependent Upregulation of xCT Modulates the Sensitivity of T24 Bladder Carcinoma Cells to Proteasome Inhibition [Ye P,et al. Mol Cell Biol, 2014, 34(18):3421-34] PubMed: 25002527

PI3K-dependent multiple myeloma cell survival is mediated by the PIK3CA isoform. [Hofmann C, et al. Br J Haematol, 2014, 166(4):529-39] PubMed: 24766330

Mechanistic insights into the enhancement of adeno-associated virus transduction by proteasome inhibitors [Mitchell AM,et al. J Virol, 2014, 87(23):13035-41] PubMed: 24027330

CRM1 Inhibition Sensitizes Drug Resistant Human Myeloma Cells to Topoisomerase II and Proteasome Inhibitors both In Vitro and Ex Vivo [Turner JG,et al. J Cancer, 2014, 4(8):614-25] PubMed: 24155773

The contribution of the autophagy-lysosomal and ubiquitin-proteasomal proteolytic systems to total proteolysis in rainbow trout (Oncorhynchus mykiss) myotubes [Seiliez I, et al. Am J Physiol Regul Integr Comp Physiol, 2014, 307(11):R1330-7] PubMed: 25274907

Regulation of dimethyl-fumarate toxicity by proteasome inhibitors [Booth L, et al. Cancer Biol Ther, 2014, 15(12):1646-57] PubMed: 25482938

Combined treatment of carfilzomib and z-VAD-fmk inhibits skeletal proteolysis and apoptosis and ameliorates cancer cachexia. [Wang Q, et al. Med Oncol, 2015, 32(4):538] PubMed: 25737433

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