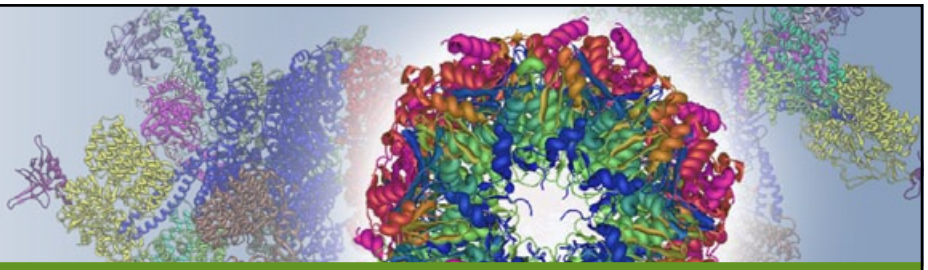
AdipoGen®

Connecting Immunology to Metabolism™



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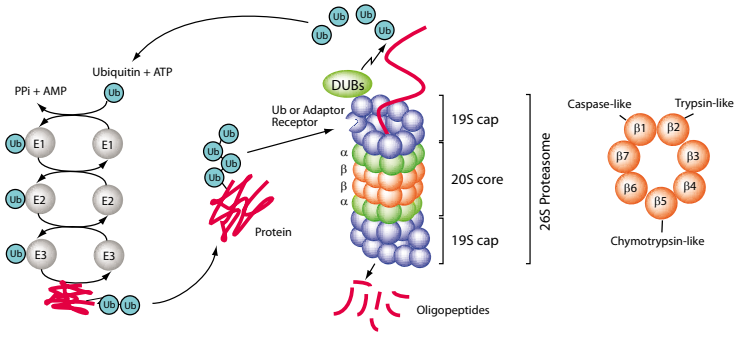
The Ubiquitin-Proteasome System (UPS)



The **ubiquitin-proteasome system (UPS)** and the autophagic-lysosomal pathway are the two major **degradation systems** for both native and misfolded proteins in eukaryotic cells, which do not act independently from each other. Defective autophagy results in accumulation of ubiquitinated proteins, impacting the flux of the UPS, while dysfunction of the UPS can promote a compensatory induction of autophagy. Through protein degradation and the maintenance of protein homeostasis, the UPS regulates many normal cellular processes including signal transduction, cell cycle control, transcription, inflammation and apoptosis. The regulated proteolysis of bulk and misfolded proteins is strictly controlled by the 26S proteasome complex.

The **26S proteasome** complex recognizes polyubiquitinated proteins, which were marked for elimination by the E1, E2 and E3 ubiquitinating enzymes (see Figure). Upon recognition, unfolding and transfer of the de-ubiquitinated target protein by the **19S regulatory cap** into the interior of the cylindrical **20S proteasome core** particle, protein degradation is facilitated by catalytic β-subunits having nucleophilic N-terminal threonine (Thr1) residues. Although eukaryotic 20S proteasomes harbor seven different β-subunits in their two-fold symmetrical α7β7β7α7 stacked complexes, only three β-subunits per β-ring **[subunits β1 (caspase-like), β2 (trypsin-like) and β5 (chymotrypsin-like)]** are proteolytically active. These three β-subunits are major targets for small molecule proteasome inhibitors. The blockade or inactivation of the 26S proteasome complex-regulated degradative process, using small molecule inhibitors against one or more catalytic β-subunits, can lead to significant build-up of cytotoxic proteins. Subsequently, apoptotic pathways are activated, particularly in rapidly proliferating cells. **Proteasome inhibition** has therefore implications in a number of human diseases such as cancer, inflammation and ischemic stroke and is an important therapeutic target.

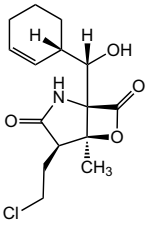
NEW

Salinosporamide A – *A Potent 20S Proteasome Inhibitor*

Salinosporamide A [SalA; Marizomib; NPI-0052; ML858]

AG-CN2-0444-C100 100 µg

Formula: $C_{15}H_{20}ClNO_4$ **MW:** 313.8 **CAS:** 437742-34-2



Potent, irreversible inhibitor of all the three proteolytic activities of the mammalian 20S proteasome.

- β5-subunit: chymotrypsin-like (EC_{50} = 3.5nM)
- β2-subunit: trypsin-like (EC_{50} = 28nM)
- β1-subunit: caspase-like or peptidyl-glutamyl peptide-hydrolyzing (PGPH) (EC_{50} = 430nM)

LIT: Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus salinospora: R.H. Feling, et al.; Angew. Chem. Int. Ed. Engl. **42,** 355 (2003) • Discovery and development of the anticancer agent salinosporamide A (NPI-0052): W. Fenical, et al.; Bioorg. Med. Chem. **17,** 2175 (2009) • Salinosporamide natural products: Potent 20S proteasome inhibitors as promising cancer chemotherapeutics: T.A. Gulder & B.S. Moore; Angew. Chem. Int. Ed. Engl. **49,** 9346 (2010) (Review)

THE STANDARD

Standard Proteasome Inhibitors – *From the Source!*

PRODUCT NAME	DESCRIPTION	PID
Salinosporamide A	Inhibits all three catalytic activities: chymotrypsin-like (EC_{50} = 3.5nM); trypsin-like (EC_{50} = 28nM); caspase-like (EC_{50} = 430nM).	AG-CN2-0444
Bortezomib [PS-341]	Chymotrypsin-like and caspase-like activity inhibitor.	AG-CR1-3602
Epoxomicin	Predominant chymotrypsin-like activity inhibitor.	AG-CN2-0422
clasto-Lactacystin β-lactone	Chymotrypsin-like, trypsin-like and caspase-like activity inhibitor.	AG-CN2-0442
Lactacystin	Chymotrypsin-like, trypsin-like and caspase-like activity inhibitor.	AG-CN2-0104
Z-Leu-Leu-Phe-CHO [MG-110]	Chymotrypsin-like activity inhibitor.	AG-CP3-0021
Z-Leu-Leu-Nva-CHO [MG-115]	Chymotrypsin-like activity inhibitor.	AG-CP3-0015
Z-Leu-Leu-Leu-CHO [MG-132]	Chymotrypsin-like and caspase-like activity inhibitor.	AG-CP3-0011
Z-Leu-Leu-Leu-B(OH)2 [MG-262]	Chymotrypsin-like and caspase-like activity inhibitor.	AG-CP3-0024
b-AP15 [DUB Inhibitor] Solution	Inhibitor of the 19S deubiquitinases (DUBs), ubiquitin-specific-processing protease 14 (USP14) and ubiquitin c-terminal hydrolase isozyme L5 (UCHL5).	AG-CS1-0102

Proteasome Modulators

Betulinic acid (>99%)	Chymotrypsin-like activity activator at low micromolar concentration.	AG-CN2-0415
Betulinic acid (>97%)	Chymotrypsin-like activity activator at low micromolar concentration.	AG-CN2-0417
Curcumin (high purity)	Inhibits all three catalytic activities (IC_{50}~10μM).	AG-CN2-0059
(-)-Epigallocatechin gallate [EGCG]	Chymotrypsin-like activity inhibitor (IC_{50}~200nM).	AG-CN2-0063
Quercetin . dihydrate	Inhibits all three catalytic activities (IC_{50}~15μM).	AG-CN2-0409
Terrein	Chymotrypsin- and trypsin-like activity inhibitor (IC_{50}~0.3mM).	BVT-0193

Fluorescent Probes for Proteasome Activity Measurement

Me_4BodipyFL-Ahx$_3$Leu$_3$VS	Cell permeable fluorescent proteasome activity probe.	AG-CR1-3601
Ac-Arg-Leu-Arg-AMC	Fluorogenic substrate for the trypsin-like activity of the 20S proteasome.	AG-CP3-0013
Boc-Leu-Arg-Arg-AMC	Fluorogenic substrate for the trypsin-like activity of the 20S proteasome.	AG-CP3-0014
Suc-Leu-Leu-Val-Tyr-AMC	Fluorogenic substrate for measuring the chymotrypsin-like activity of the 20S proteasome.	AG-CP3-0016
Suc-Leu-Tyr-AMC	Fluorogenic substrate for the chymotrypsin-like activity of the 20S proteasome.	AG-CP3-0017
Z-Leu-Leu-Leu-AMC	Fluorogenic substrate for the chymotrypsin-like activity of the 20S proteasome.	AG-CP3-0019
Z-Leu-Leu-Glu-AMC	Fluorogenic substrate for the caspase-like activity of the 20S proteasome.	AG-CP3-0022

Proteasome Complex Reagents

PRODUCT NAME	PID
19S Proteasome (human)	AG-40T-0200
19S Proteasome-UCHL5 (C88A) (human)	AG-40T-0201
20S Immunoproteasome (dog)	AG-40T-0202
20S Immunoproteasome (human)	AG-40T-0203
20S Immunoproteasome (mouse)	AG-40T-0204
20S Immunoproteasome (rat)	AG-40T-0205
20S Proteasome (dog)	AG-40T-0206
20S Proteasome (human)	AG-40T-0207
20S Proteasome (mouse)	AG-40T-0208
20S Proteasome (rabbit)	AG-40T-0209
20S Proteasome (rat)	AG-40T-0211
26S Proteasome (human)	AG-40T-0212

PRODUCT NAME	PID
20S Proteasome Assay Kit (SDS Activation Format)	AG-44T-0100
20S Proteasome Activation Solution (100X)	AG-10T-0010
20S Proteasome Reaction Buffer (20X)	AG-10T-0019
Angiocidin (human) (rec.)	AG-40B-0061
Angiocidin (human) (rec.) (Agarose)	AG-40T-0216
Angiocidin (human) (rec.) (Biotin)	AG-40T-0217B
Angiocidin (human) (rec.) (His)	AG-40T-0219
Angiocidin (UIM domains) Peptide (rec.) (Agarose)	AG-40T-0220
PA28 Activator (α-subunit) (human) (rec.)	AG-40T-0315
PA28 Activator (α-subunit) (rat) (rec.)	AG-40T-0316
PA28 Activator (β-subunit) (human) (rec.)	AG-40T-0317
PA28 Activator (γ-subunit) (human) (rec.) (His)	AG-40T-0318

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