

Autophagy

Modulators of Autophagy Signaling

Autophagy represents a homeostatic cellular mechanism for the turnover of organelles and proteins through a lysosome-dependent degradation pathway. Misfolded or aggregated proteins are removed, damaged organelles such as mitochondria, endoplasmic reticulum and peroxisomes are cleared and intracellular pathogens are eliminated. During starvation, autophagy facilitates cell survival through the recycling of metabolic precursors.

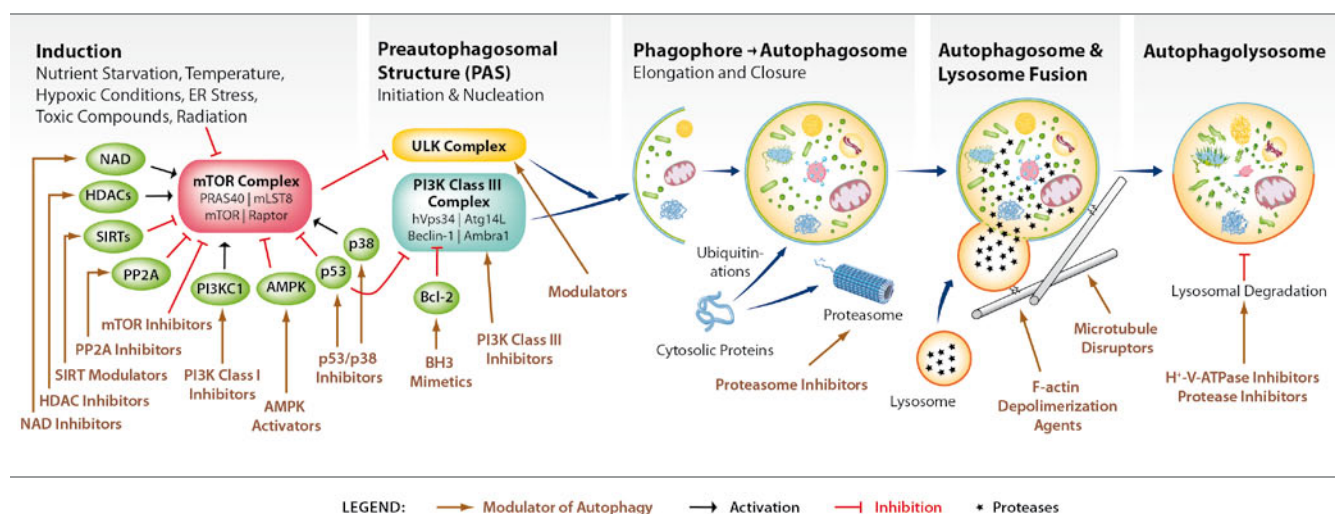
There are three defined types of autophagy: **macroautophagy**, **microautophagy** and **chaperone-mediated autophagy**, all of which promote proteolytic degradation of cytosolic components at the lysosome. **Macroautophagy** delivers cytoplasmic cargo through the intermediary of a double membrane-bound vesicle, referred to as an autophagosome, that fuses with the lysosome to form an autophagolysosome (see Figure). The autophagosomal contents are degraded by lysosomal acid proteases. Amino acids and other small molecules that are generated by autophagic degradation are delivered back to the cytoplasm for recycling or energy production.

Autophagy has been recognized as an essential function for cell homeostasis and adaptation to environmental stress conditions, including nutritional starvation, energy

depletion, endoplasmic reticulum stress, oxidative stress and hypoxia. Despite the widely accepted role for autophagy in **cellular survival**, it also has been associated with the regulation of various **cell death pathways**, including regulated (e.g. apoptosis, pyroptosis, and necroptosis) and catastrophic (e.g. necrosis) types of cell death. Furthermore it plays a vital role in **innate and adaptive immune mechanisms**. Recent advances suggest that autophagy can dampen inflammatory responses, including **inflammasome**-dependent caspase-1 activation and maturation of proinflammatory cytokines. Taken together, autophagy might play a key role in preventing diseases such as cancer, neurodegeneration, cardiomyopathy, diabetes, liver disease, autoimmune diseases and infections. Strategies aiming to modulate autophagy, such as small molecule activators and inhibitors, might help to elucidate the biological processes behind.

SELECTED REVIEWS: Methods in mammalian autophagy research: N. Mizushima, et al; Cell 140, 313 (2010) • Regulation of Autophagy by Kinases: S.Sridharan, et al; Cancers 3, 2630 (2011) • Autophagy modulation as a potential therapeutic target for diverse diseases: D.C. Rubinsztein, et al; Nat. Rev. Drug Discov. 11, 709 (2012) • The Impact of Autophagy on Cell Death Modalities: S.W. Ryter, et al; Int. J. Cell Biol. 2014, 502676 (2014)

Schematic overview on mammalian macroautophagy, including selected physiological and small molecule modulators

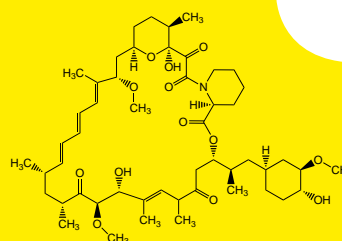


mTOR Complex Modulators

Rapamycin [Sirolimus] – Potent mTOR Inhibitor

AG-CN2-0025

100 µg | 1 mg | 5 mg | 25 mg

Formula: C₅₁H₇₉NO₁₃**MW:** 914.2**CAS:** 53123-88-9**BULK**

PRODUCT NAME	ACTIVITY	EFFECT ON AUTOPHAGY	PID	SIZE
Rapamycin	mTOR Inhibitor	Activator	AG-CN2-0025	100 µg 1 mg 5 mg 25 mg
PK 11195	mTOR Modulator	Modulator	AG-CR1-0008	10 mg 50 mg
AICAR	AMPK Activator & mTOR Inhibitor	Activator	AG-CR1-0061	10 mg 50 mg 100 mg
(-)-Epigallocatechin gallate	AMPK Activator & Proteasome Inhibitor	Activator	AG-CN2-0063	25 mg 100 mg
Piceatannol	AMPK Activator & PI3K Class I inhibitor	Activator	AG-CN2-0086	1 mg 5 mg 25 mg
Resveratrol	AMPK Activator / SIRT1 Activator	Activator	AG-CN2-0033	50 mg 100 mg 500 mg
Saquinone	AMPK Activator	Activator	AG-CN2-0032	1 mg 5 mg
Apicidin	HDAC Inhibitor	Activator	AG-CN2-0087	1 mg 5 mg
MS-275	HDAC1 Inhibitor	Activator	AG-CR1-0032	1 mg 5 mg 25 mg
Splitomicin	Yeast HDAC Sir2p Inhibitor	Activator	AG-CR1-0088	1 mg 5 mg 25 mg
Trichostatin A	HDAC Inhibitor	Activator	AG-CN2-0108	1 mg 5 mg
FK-866	Nampt Inhibitor / NAD Depletion	Activator	AG-CR1-0011	1 mg 5 mg
CHS-828 [GMX1778]	Nampt Inhibitor / NAD Depletion	Activator	AG-CR1-0064	5 mg 25 mg
SB202190	p38 MAP Kinase Inhibitor	Activator	AG-CR1-0028	1 mg 5 mg 25 mg
Pifithrin-α (cyclic) . HBr	p53 Inhibitor	Inhibitor	AG-CR1-0052	5 mg 10 mg 50 mg
Pifithrin-α . HBr	p53 Inhibitor	Inhibitor	AG-CR1-0004	5 mg 10 mg 25 mg
Eupatilin	PI3K Class I Inhibitor	Activator	AG-CN2-0432	5 mg 25 mg
Luteolin	PI3K Class I Inhibitor	Activator	AG-CN2-0098	5 mg 25 mg
3-Methyladenine	PI3K Class I & Class III Inhibitor	Activator/ Inhibitor	AG-CR1-3597	25 mg 100 mg 250 mg
S14161	PI3K Class I Inhibitor	Activator	AG-CR1-3516	1 mg 5 mg
Cytostatin	PP2A Inhibitor	Inhibitor	AG-CN2-0093	250 µg
Fostriecin	PP2A Inhibitor	Inhibitor	AG-CN2-0057	10 µg
Okadaic acid (high purity) <i>Other salt forms available!</i>	PP2A Inhibitor	Inhibitor	AG-CN2-0056	25 µg 100 µg 1 mg
Rubratoxin A	PP2A Inhibitor	Inhibitor	AG-CN2-0092	250 µg 500 µg
Thapsigargin	SERCA Inhibitor	Activator	AG-CN2-0003	1 mg 5 mg 10 mg 25 mg
Quercetin . 2H ₂ O	SIRT1 Activator / PI3K Class I Inhibitor	Activator	AG-CN2-0409	1 g 5 g
Suramin . 6Na	SIRT1 & ATPase Inhibitor	Inhibitor	AG-CR1-3575	50 mg 250 mg 1 g

BULK available!

Proteasome Inhibitors

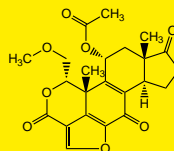
PRODUCT NAME	ACTIVITY	EFFECT ON AUTOPHAGY	PID	SIZE
Epoxomicin	Proteasome Inhibitor	Activator	AG-CN2-0422	100 µg 500 µg
Lactacystin	Proteasome Inhibitor	Activator	AG-CN2-0104	100 µg 200 µg 500 µg 1 mg
MG-132	Proteasome Inhibitor	Activator	AG-CP3-0011	1 mg 5 mg 25 mg

Preautophagosome (PAS)/Nucleation Modulators

Wortmannin – Potent PI3K Inhibitor

AG-CN2-0023

1 mg | 5 mg | 25 mg

Formula: C₂₃H₂₄O₈ | **MW:** 428.4 | **CAS:** 19545-26-7

BULK

PRODUCT NAME	ACTIVITY	EFFECT ON AUTOPHAGY	PID	SIZE
LY-294,002	PI3K Class III & Class I Inhibitor	Inhibitor / Activator	AG-CR1-0108	1 mg 5 mg 25 mg
3-Methyladenine	PI3K Class III & Class I Inhibitor	Inhibitor / Activator	AG-CR1-3597	25 mg 100 mg 250 mg
Viridiodiol	PI3K Class III & Class I Inhibitor	Inhibitor / Activator	AG-CN2-0126	250 µg 1 mg
Wortmannin	PI3K Class III & Class I Inhibitor	Inhibitor / Activator	AG-CN2-0023	1 mg 5 mg 25 mg
PD 150,606	Calpain Inhibitor	Activator	AG-CR1-0066	5 mg 25 mg

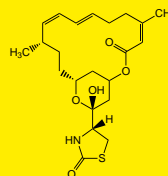
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Autophagosome-Lysosome Fusion & Degradation Modulators

Latrunculin A – F-actin Depolymerization Agent

AG-CN2-0027

100 µg | 500 µg

Formula: C₂₂H₃₁NO₅S | **MW:** 421.6 | **CAS:** 76343-93-6

BULK

PRODUCT NAME	ACTIVITY	EFFECT ON AUTOPHAGY	PID	SIZE
Dynasore	Dynamin Inhibitor	Lys/AutoFusion Inhibitor	AG-CR1-0045	5 mg 25 mg
Jasplakinolide	F-actin Stabilization	Modulator	AG-CN2-0037	50 µg 100 µg
Latrunculin A	F-actin Depolymerization	Lys/AutoFusion Inhibitor	AG-CN2-0027	100 µg 500 µg
Latrunculin B	F-actin Depolymerization	Lys/AutoFusion Inhibitor	AG-CN2-0031	1 mg
16- <i>epi</i> -Latrunculin B	F-actin Depolymerization	Lys/AutoFusion Inhibitor	AG-CN2-0034	100 µg
Swinholide A	F-actin Inhibitor	Lys/AutoFusion Inhibitor	AG-CN2-0035	10 µg 50 µg
Troglitazone	Rab7 Inhibitor	Lys/AutoFusion Inhibitor	AG-CR1-3565	5 mg 25 mg
Nocodazole	Microtubule Inhibitor	Lys/AutoFusion Inhibitor	AG-CR1-0019	5 mg 10 mg 25 mg 50 mg
Colcemid	Microtubule Inhibitor	Lys/AutoFusion Inhibitor	AG-CR1-3567	1 mg 5 mg
Colchicine	Microtubule Inhibitor	Lys/AutoFusion Inhibitor	AG-CN2-0048	500 mg 1 g
Curvulin	Microtubule Inhibitor	Lys/AutoFusion Inhibitor	BVT-0097	1 mg 5 mg
Ferulenol	Microtubule Stimulator	Modulator	AG-CN2-0011	1 mg 5 mg 10 mg
Ilimaquinone	Microtubule Inhibitor	Lys/AutoFusion Inhibitor	AG-CN2-0038	100 µg
Pseudolaric acid B	Microtubule Inhibitor	Modulator	AG-CN2-0083	100 µg 1 mg
Thiocolchicine	Microtubule Inhibitor	Lys/AutoFusion Inhibitor	AG-CN2-0074	5 mg 25 mg
Bafilomycin A1	H ⁺ V-ATPase Inhibitor	Lysosomal Degradation Inhibitor	BVT-0252	100 µg 1 mg
Bafilomycin B1	H ⁺ V-ATPase Inhibitor	Lysosomal Degradation Inhibitor	BVT-0004	100 µg 1 mg 5 mg
Bafilomycin C1	H ⁺ V-ATPase Inhibitor	Lysosomal Degradation Inhibitor	BVT-0068	1 mg
Concanamycin A	H ⁺ V-ATPase Inhibitor	Lysosomal Degradation Inhibitor	BVT-0237	25 µg 100 µg 1 mg
Concanamycin B	H ⁺ V-ATPase Inhibitor	Lysosomal Degradation Inhibitor	BVT-0253	25 µg 100 µg 500 µg
Concanamycin C	H ⁺ V-ATPase Inhibitor	Lysosomal Degradation Inhibitor	BVT-0254	25 µg 100 µg 500 µg

Other Autophagy Modulators

PRODUCT NAME	PID	EFFECT ON AUTOPHAGY
Betulinic acid (>99%)	AG-CN2-0415	Activator
FTY720 . HCl	AG-CR1-3587	Activator
Genistein	AG-CN2-0427	Activator
Loxoribine	AG-CR1-3584	Activator
Q-VD-OPh	AG-CP3-0006	Activator
Z-VAD-FMK (Cell permeable)	AG-CP3-0002	Activator
Z-VRPR-FMK	AG-CP3-0008	Activator

PRODUCT NAME	PID	EFFECT ON AUTOPHAGY
Cyclosporin A	AG-CN2-0079	Inhibitor
Forskolin	AG-CN2-0089	Inhibitor
Necrostatin-1	AG-CR1-2900	Inhibitor
Curcumin (high purity)	AG-CN2-0059	Modulator
Nigericin . Na	AG-CN2-0020	Modulator
PP2	AG-CR1-3563	Modulator
Wogonin	AG-CN2-0064	Modulator

Newly Released Autophagy Proteins

PRODUCT NAME	SOURCE	PURITY	PID	SIZE
ATG3 (human) (rec.) (His)	E. coli	≥95% (SDS-PAGE)	AG-40B-0141	50 µg 3 x 50 µg
Beclin-1 (human) (rec.) (His)	E. coli	≥85% (SDS-PAGE)	AG-40B-0140	10 µg 5 x 10 µg

Ageladine – Novel Non-toxic, Cell Permeable, pH-dependent Fluorescent Dye for Live Imaging

Ageladine A (synthetic)

AG-CMA-1001-C200

200 µg

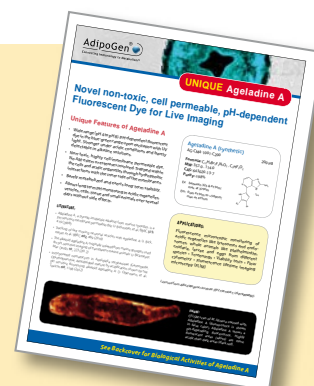
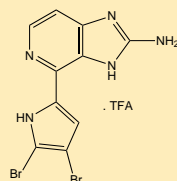
Formula: C₁₂H₈Br₂F₃N₅O₂ · C₂HF₃O₂

MW: 357.0 . 114.0

CAS: 643020-13-7

Purity: ≥98%

Ex: between 325 & 415nm; max. at 370nm
Em: from 415nm to >500nm; max. at 415nm



LITERATURE: Ageladine A, a pyrrole-imidazole alkaloid from marine sponges, is a pH sensitive membrane permeable dye: U. Bickmeyer, et al; *BBRC* **373**, 419 (2008)

Unique Features

- Wide range (pH 4 to pH 8). pH-dependent fluorescent dye in the blue-green range upon excitation with UV light. Stronger under acidic conditions and barely detectable in alkaline solutions.
- Non-toxic, highly cell/membrane permeable dye. No AM-esters or esterases involved. Trapped within the cells and acidic organelles through hydrophobic interactions with the inner side of the membranes.
- Barely metabolized and exerts long-term stability.
- Allows long term pH monitoring in acidic organelles, vesicles, cells, tissue and small animals over several days without side effects.

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