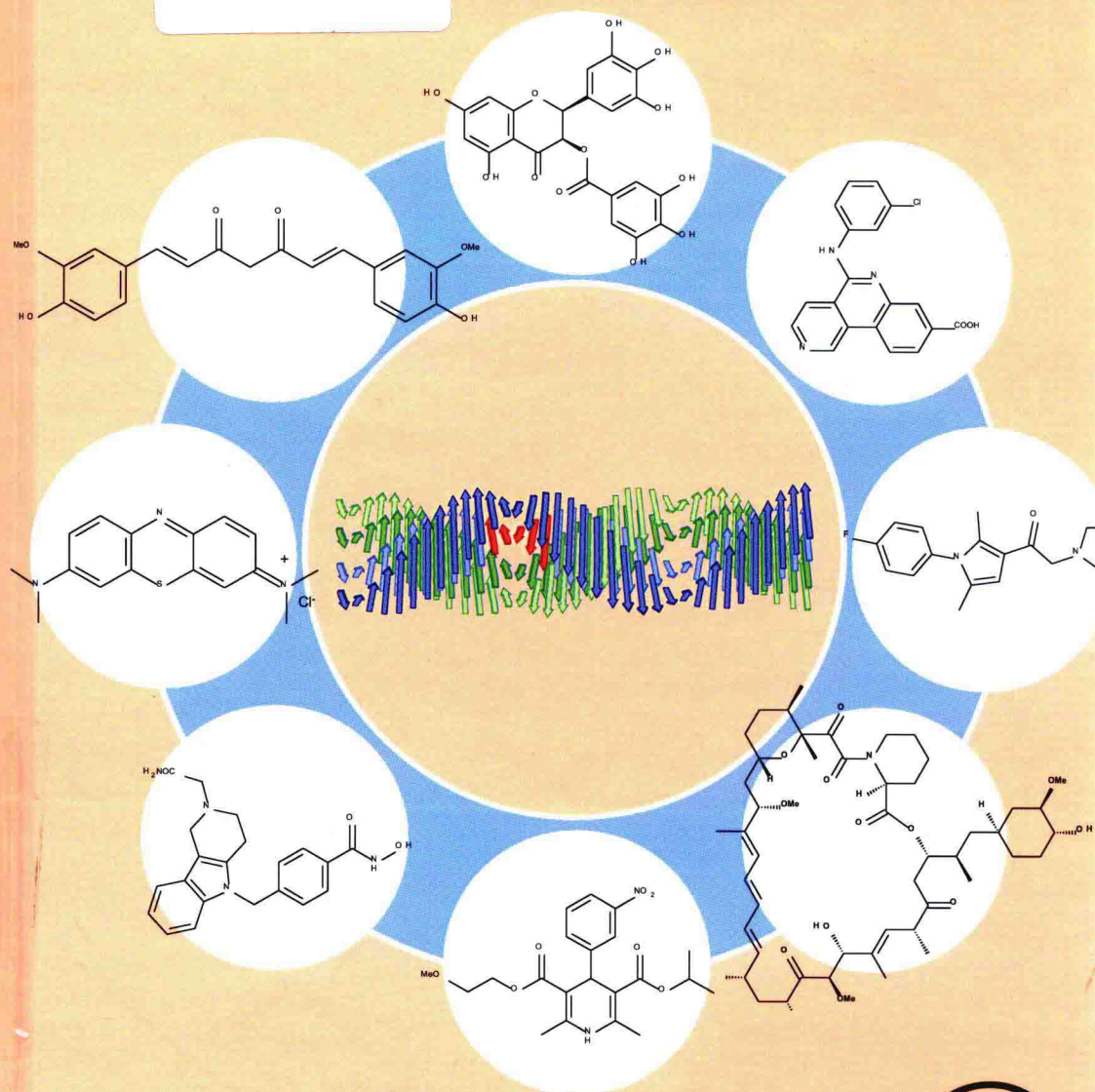
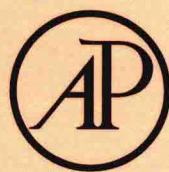


Chemical Modulators of Protein Misfolding and Neurodegenerative Disease



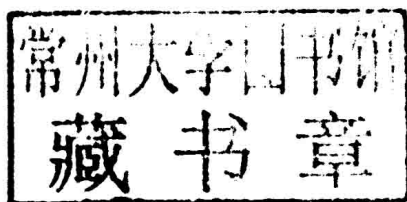
Pierfausto Seneci



CHEMICAL MODULATORS OF PROTEIN MISFOLDING AND NEURODEGENERATIVE DISEASE

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CHEMICAL MODULATORS
OF PROTEIN MISFOLDING
AND NEURODEGENERATIVE
DISEASE

Dedication

To Hanno, the king of contrarians: I owe you.

Abbreviations

15-DSG	15-deoxyspergualin
17-DMAG	N,N-dimethylaminoethyl-17-demethoxy geldanamycin
5-HT	serotonin/5-hydroxytryptamine
6-OHDA	6-OH dopamine
AA	aminoacid
AAG	17-allylamino-17-demethoxy geldanamycin
A β	amyloid β
ABAD	amyloid-binding alcohol dehydrogenase
Abl	Abelson kinase
ACD	α -crystallin domain
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADAM10	α -secretase disintegrin and metalloproteinase domain 10
ADMET	adsorption, distribution, metabolism, excretion, toxicity
ADNP	activity-dependent neuroprotective protein
ADP	adenosine diphosphate
AE	adverse event
AF	atrial fibrillation
AFM	atomic force microscopy
AICD	APP intracellular domain
Akt	protein kinase B
ALS	amyotrophic lateral sclerosis
AMBRA1	autophagy/beclin 1 regulator 1
AmF	amyloid fiber
AMP	adenosine monophosphate
AMPK	AMP-mediated protein kinase
APs	autophagosomes
APAF-1	apoptosis protease activating factor 1

APIase	aminopeptidyl isomerase
ApoE4	apolipoprotein E4
APP	amyloid precursor protein
ARE	antioxidant response element
Atg	autophagy-related gene
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
ATPZ	aminothienopyridazine
ATR	ataxia telangiectasia mutated and RAD3-related
BACE-1	β -APP cleaving enzyme, β -secretase 1
BAG	Bcl-2-associated athanogene
BARD	BRCA1-associated RING domain protein
BBB	blood-brain barrier
BCR	breakpoint cluster region
BRCA1	breast cancer type 1
BTA	benzothiazole aniline
BuChE	butyl cholinesterase
CAMKK β	calmodulin-activated kinase kinase β
CamKII	Ca ²⁺ /calmodulin-dependent protein kinase II
cAMP	cyclic AMP
cdc37	cell division cycle 37 homolog
cdc4	cell division control protein 4
Cdk	cyclin-dependent kinase
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
CHIP	C-terminus of Hsc70 interacting protein
CIA	collagen induced arthritis
cIAP	cellular inhibitor of apoptosis protein
CK2	casein kinase 2
CMA	chaperone-mediated autophagy
CML	chronic myeloid leukemia
CMT	Charcot-Marie-Tooth disease
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COS-7	CV-1 in origin SV40-carrying
CP	core particle

CRBN	cereblon
CSF	cerebrospinal fluid
CTF	C-terminal fragment
Cul	cullin
Δ^9 -THC	Δ^9 -tetrahydrocannabinol
D1R	dopamine receptor 1
DDBP1	damaged DNA binding protein 1
DHA	docosahexaenoic acid
DHP	dihydropyrimidine
DLB	dementia with Lewy bodies
DMB	dynein motor binding
DPBP	diphenylbutylpiperidine
DPmT	dual PI3K/mTOR
DUB	deubiquitinating enzyme
DYRK1A	dual specificity tyrosine-phosphorylation-regulated kinase 1A
E	enzymes
E1	UBQ-activating enzyme
E2	UBQ-conjugating enzyme
E3	UBQ ligase
E4	UBQ chain assembly factor
E6AP	E6-associated protein
ECG	epicatechin-3-gallate
EGFR	epidermal growth factor receptor
EGCG	epigallocatechin-3-gallate
EIF4E-BP1	eukaryotic translation initiation factor 4
	epsilon binding protein 1
Epac	exchange protein directly activated by cAMP
EpoD	epothilone D
EPR	electron paramagnetic resonance
ER	endoplasmic reticulum
ERK	extracellular-regulated signal kinase
ES	endosome
EXP1	exported protein 1
FCA	Freund's complete adjuvant
FKBP	FK-binding protein
FL	full length

FLICE	FADD-like interleukin-1 beta-converting enzyme
FLIP	FLICE inhibitory protein
Foxp3 ⁺	forkhead box P3
FRB	FKBP–rapamycin binding
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
FUS	fused in sarcoma
GA	gambogic acid
GAP-43	growth-associated protein 43
GFP	green fluorescent protein
GlcNAc	N-acetyl-D-glucosamine
GOF	gain-of-function
GR	glucocorticoid receptor
GSI	γ-secretase inhibitor
GSK-3	glycogen synthase kinase 3
GSM	γ-secretase modulator
GSPE	grape seed polyphenolic extract
GSR	glutathione disulfide reductase
GTP	guanosine triphosphate
HAA	hardwickiic acid
HCC	hepatocellular carcinoma
HCS	high content screen
HCT116	human colon carcinoma
HD	Huntington disease
HDAC	histone deacetylase
HDM2	human double minute 2 homolog
HECT	homologous to the E6AP carboxyl terminus
HEK	human embryonic kidney
hERG	human ether-a-go-go related gene
HGPS	Hutchinson–Gilford progeria syndrome
HIF-1α	hypoxia factor 1α
HIV	human immunodeficiency virus
Hop	Hsp70-Hsp90 organizing protein
HP	hyperphosphorylation, hyperphosphorylated
H2R	histamine receptor 2
Hsc	heat-shock constitutive

HSF1	heat shock factor 1
HSP	heat shock protein
HspB1	Hsp70-binding protein 1
HT	high throughput
Htt	huntingtin
HTS	high-throughput screening
HuR	human antigen R
HX-MS	hydrogen exchange mass spectrometry
I1R	imidazoline 1 receptor
IAP	inhibitor of apoptosis protein
IC	ion channel
i.c.v.	intracerebroventricular
IC ₅₀	inhibitory concentration, 50% inhibition
IDE	insulin-degrading enzyme
IFN- β	interferon β
IGF-1	insulin growth factor 1
IKK	I kappa B kinase
IL	interleukin
IND	investigational new drug
iNOS	inducible nitric oxide synthase
i.p.	intraperitoneal
IP3	inositol triphosphate
IQA	indoloquinazoline acetic acid
IRE1	inositol-requiring protein 1
IRS1	insulin receptor signaling 1
ISF	interstitial fluid
ITC	isothermal calorimetry
i.v.	intravenous
JAK	Janus-activated kinase
JNK	c-jun N-terminal kinase
K _D	dissociation constant
kDa	kilodalton
Keap-1	kelch-like ECH-associated protein 1
K _i	inhibition constant
KIR	keap1-interacting region
KO	knockout
LC	liquid chromatography

LC3	light chain 3
LD	lipid droplet
LIR	LC3-interacting region
LMT	leucomethylene blue
LOF	loss-of-function
LPS	lipopolysaccharide
LS	lysosome
MA	macroautophagy
MALDI	matrix assisted laser desorption ionization
MAP	microtubule-associated protein
MAPK	mitogen-activated protein kinase
mAtg	mammalian autophagy-related gene
MB	methylene blue
MCI	mild cognitive impairment
MCL-1	myeloid cell leukemia sequence 1
MEFs	murine embryonic fibroblasts
MEK	MAP2K, MAPKK, mitogen-activated protein kinase kinase
MEKK3	mitogen-activated kinase kinase kinase 3
MIC	minimal inhibitory concentration
MK2	mitogen-activated protein kinase-activated protein kinase 2
μ M	micromolar
MMP	matrix metalloproteinase
MOK	MAPK/MAK/MRK-overlapping kinase
MPP ⁺	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	mass spectrometry
MSA	multiple system atrophy
MT	microtubule
MTBR	MT-binding repeat
mTORC	mammalian target of rapamycin complex
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NBD	nucleotide-binding domain
NCI	National Cancer Institute
NDD	neurodegenerative disease

NEF	nuclear exchange factor
NEP	neprilysin
NET	norepinephrine transporter
NIH	National Institute of Health
NF- κ B	nuclear factor kappa-light-chain-enhancer of activated B cells
NFTs	neurofibrillary tangles
NIH	National Institute of Health
nM	nanomolar
NMDA	N-methyl-D-aspartate
NMR	nuclear magnetic resonance
NO	nitric oxide
Nrf2	NF-E2-related factor 2
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OGA	O-GlcNAc hydrolase
OGT	O-GlcNAc transferase
OKA	okadaic acid
OPCA	OPR/PC/AID
OPN	optineurin
PAS	phagophore assembly site
PB1	phox and bem 1p
PcTS	phthalocyanine tetrasulfonate
PD	Parkinson's disease
PDB	Paget's disease of bone
PDE	phosphodiesterase
PKD1	3-phosphoinositide-dependent kinase 1
PDS-95	post-synaptic density protein 95
PDy	pharmacodynamic
PE	phosphatidylethanolamine
PEG	polyethyleneglycol
PES	pifithrin- μ
PET	positron emission tomography
PG	prostaglandin
Pgp	P-glycoprotein
PHF	paired helical filament
PI	phosphatidylinositol

PI3K	phosphatidylinositol-3-kinase
PI3P	phosphatidylinositol-3-phosphate
PiB	Pittsburgh B
PK	pharmacokinetic
PKC	protein kinase C
PKR	protein kinase R
PLA	polylactic acid
PLC	phospholipase C
PLGA	poly-(lactic-co-glycolic acid)
PLpro	papain-like protease
p.o.	<i>per os</i> , oral
PolyQ	polyglutamine
PP2A	protein phosphatase 2A
PPAR γ	peroxisome proliferator-activated receptor γ
PPI	protein–protein interaction
PQC	protein quality control
PrP	prion protein
Prx	peroxiredoxin
PSEN	presenilin
PSP	progressive supranuclear palsy
PTH	phenylthiazolyl hydrazide
PTM	post-translational modification
QSAR	quantitative structure–activity relationship
R	receptor
Rab	ras-related in brain
Raf	rapid accelerated fibrosarcoma
Rag	ras-related small GTP binding protein
Rag GTPases	ras-related GTPases
RANTES	regulated on activation, normal T cell expressed and secreted
Rap2B	ras-related protein 2B
RBR	RING-in-between-RING
RDS	rhabdomyosarcoma
REDD1	regulation of DNA damage response 1 protein
RET	rearranged during transfection
RFP	red fluorescent protein
RING	really interesting new gene

ROCK	rho-associated coiled-coil kinase
ROS	reactive oxygen species
RP	regulatory particle
S6K1	S6 kinase 1
SAHA	suberoyl anhydride hydroxamic acid
SAR	structure–activity relationship
SARS	severe acute respiratory syndrome
SBD	substrate-binding domain
s.c.	subcutaneous
SCA	spinocerebellar ataxia
SCF	Skp-cullin-F-box-containing
scNB	scrapie-infected neuroblastoma
sHsp	small heat shock protein
siRNA	small interference RNA
SIRT	sirtuin
SMA	spinal muscular atrophy
Smac/DIABLO	second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI
SMER	small molecule enhancers of rapamycin
SMIR	small molecule inhibitors of rapamycin
SMN2	survival motor neuron 2
SOD1	superoxide dismutase 1
SPA	scintillation proximity assay
Spautin-1	specific and potent autophagy inhibitor-1
SPECT	single photon emission computer tomography
SPR	surface plasmon resonance
STAT	signal transducer and activator of transcription
TAI	tau aggregation inhibitor
TAR	transactive response
TBB	tetrabromobenzimidazole
TBBt	tetrabromobenzotriazole
TBI	traumatic brain injury
TBK1	TANK-binding kinase 1
TBS	TRAF6 binding site
TEM	transmission electron microscopy

TDP-43	transactive response/TAR DNA-binding protein 43
TDZD	thiadiazolidinone
TG	transgenic
TG2	transglutaminase 2
Th	thioflavin
THP	tetrahydrohyperforin
TIBI	tetraiodobenzimidazole
TMD	transmembrane domain
TNF	tumor necrosis factor
TOF	time of flight
TPPP1	tubulin polymerization-promoting protein 1
TPR	tetratricopeptide
TRAF6	TNF receptor associated factor 6
TRB3	tribbles 3
Tregs	T-regulatory cells
TSA	trichostatin A
TSC	tuberous sclerosis complex
UAF1	USP1-USP1 associated factor 1
UBA	ubiquitin-associated
UBC	ubiquitin-conjugating
UBL	ubiquitin-like
UBQ	ubiquitin
UCH	ubiquitin C-terminal hydrolase
UIS4	up-regulated in sporozoites 4
ULK	UNC-51-like kinase
UPR	unfolded protein response
UPS	ubiquitin-proteasome system
USP	ubiquitin-specific protease
Vps34	vacuolar protein sorting protein 34
WT	wild type
ZZ	zinc finger motif

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