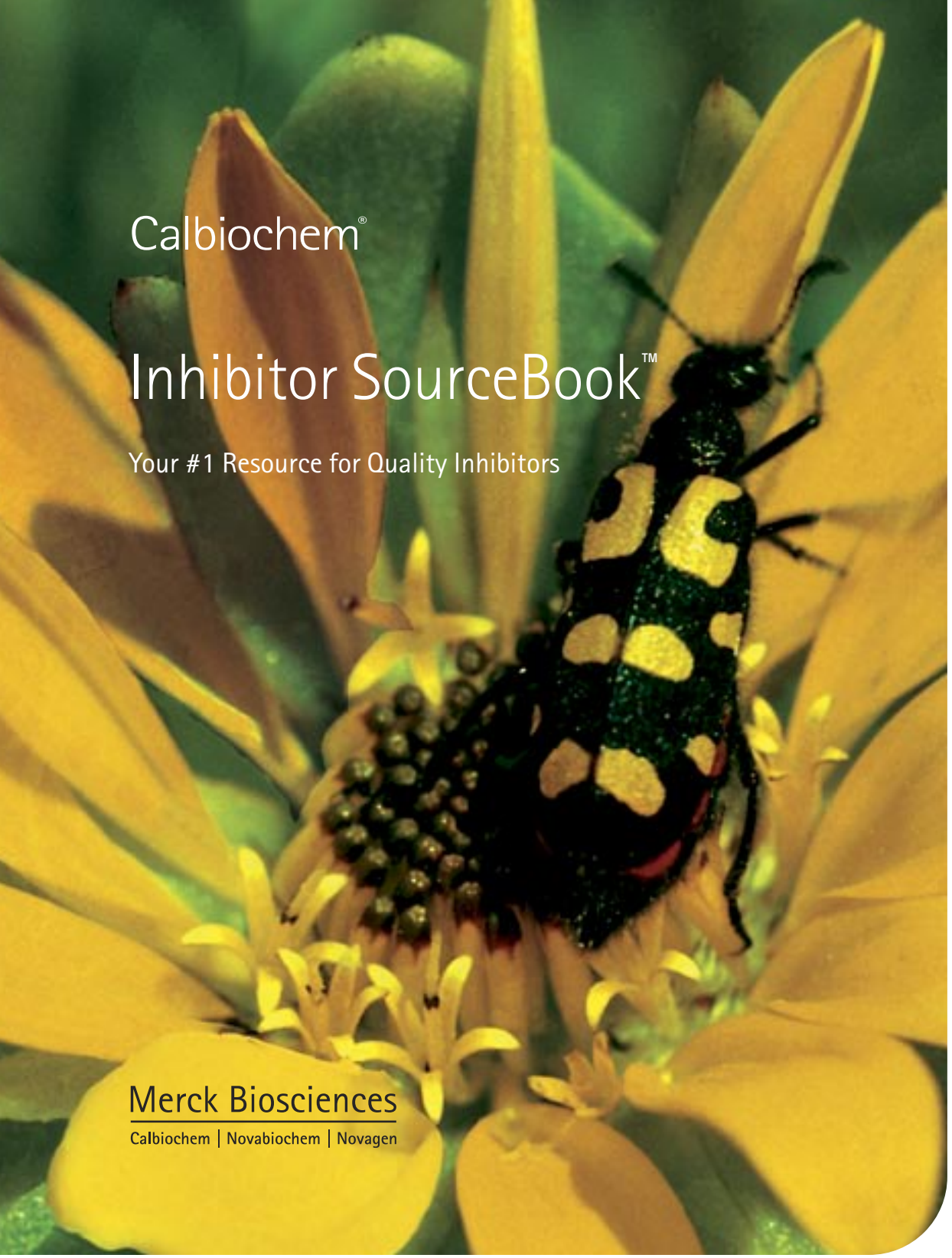

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Contents

Phosphorylation/Dephosphorylation

Akt (Protein Kinase B) Inhibitors

Akt, also known as protein kinase B (PKB), a serine/threonine kinase, is a critical enzyme in several signal transduction pathways involved in cell proliferation, apoptosis, angiogenesis, and diabetes. Four different isoforms of Akt (α, β1, β2, and γ) have been reported that differ slightly in the localization of their regulatory phosphorylation sites. Activation of Akt involves growth factor binding to a receptor tyrosine kinase and activation of PI 3-K, which phosphorylates the membrane bound $PI(4,5)P_2$ (PIP_2) to generate $PI(3,4,5)P_3$ (PIP_3). Binding of PIP_3 to Akt anchors it to the plasma membrane and exposes it to phosphorylation and activation by 3-phosphoinositide-dependent kinase-1 (PDK1). Akt is activated following its phosphorylation at two regulatory residues, a threonine residue on the kinase domain and a serine residue on the hydrophobic motif, which are structurally and functionally conserved within the AGC kinase family. Phosphorylation of threonine on the kinase domain, catalyzed by PDK1, is essential for Akt activation. Akt activity is augmented approximately 10-fold by phosphorylation at the serine on the hydrophobic motif by PDK2. Phosphorylation of Thr^{308} and Ser^{473} activates Akt α. Phosphorylation at Thr^{309} and Ser^{474} on Akt β1 and β2, and on Thr^{305} on Akt γ result in their activation. The activation of Akt is negatively regulated by PTEN, a PIP_3 specific phosphatase, and SHIP, an SH2-domain containing inositol 5-phosphatase.

The principal role of Akt in the cell is to facilitate growth factor-mediated cell survival and to block apoptotic cell death. This is achieved by phosphorylating and deactivating pro-apoptotic factors such as BAD, Caspase 9, and Forkhead transcription factors (FKHR). The phosphorylation of BAD allows it to bind to 14-3-3 protein thereby preventing localization of BAD at the mitochondria to induce apoptosis. Additionally, phosphorylation of FKHR by Akt prevents it from transcribing Fas ligand; hence it promotes cell survival. Akt also phosphorylates and activates IKKα, which leads to NF-κB activation and cell survival. Akt is also known to stimulate glycogen synthesis by phosphorylating and inactivating GSK-3 leading to the activation of glycogen synthase. The inactivation of GSK-3 also induces the up-regulation of cyclin D, which enhances cell cycle progression.

Akt is reported to play a critical role in tumorigenesis, becoming activated when tumor suppressors such as $p27^{Kip1}$ and PTEN lose their functions. Phosphorylation of p27 at Thr^{157} by Akt impairs its nuclear import and leads to its cytoplasmic accumulation. Cytoplasmic mislocalization of p27 has been strongly linked to loss of differentiation and poor outcome in breast cancer patients. Akt can also physically associate with endogenous p21, a cell cycle inhibitor, and phosphorylate it at Thr^{145}, causing its localization to the cytoplasm, ultimately resulting in deregulation of cell proliferation.

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Akt (Protein Kinase B) Inhibitors

Product	Cat. No.	Comments	Size
Akt Inhibitor	**124005**	A phosphatidylinositol ether analog that potently and selectively inhibits Akt (IC_{50} = 5.0 μM). A weak inhibitor of phosphatidylinositol 3-kinase (IC_{50} = 83 μM).	1 mg
Akt Inhibitor II (SH-5)	**124008**	A phosphatidylinositol analog that inhibits the activation of Akt and selected downstream substrates without affecting the phosphorylation of PDK-1 and other downstream kinases. Decreases phosphorylation of Akt without affecting the total Akt level.	1 mg
Akt Inhibitor III (SH-6)	**124009**	A phosphatidylinositol analog that inhibits the activation of Akt and selected downstream substrates without affecting the phosphorylation of PDK-1 and other downstream kinases. Decreases phosphorylation of Akt without affecting the total Akt level.	1 mg
NEW Akt Inhibitor IV	**124011**	A cell-permeable inhibitor of Akt phosphorylation/activation that targets ATP-binding site of a kinase upstream of Akt, but downstream of PI 3-Kinase.	1 mg 5 mg
NL-71-101	**487940**	A potent, ATP-competitive, and selective inhibitor of protein kinase B/Akt (IC_{50} = 3.7 μM). Displays 2.4-fold greater selectivity for PKB/Akt compared to protein kinase A (PKA) (IC_{50} = 9 μM).	1 mg

Calmodulin-Dependent Protein Kinase (CaM Kinase) Inhibitors

Many effects of Ca^{2+} are mediated by Ca^{2+}/calmodulin (CaM)-dependent protein kinases (CaM kinases). CaM Kinases constitute a family of structurally related enzymes that include phosphorylase kinase, myosin light chain kinase, and CaM kinases I-IV. CaM Kinase II, one of the best-studied multifunctional enzymes, is found in high concentrations in neuronal synapses, and in some regions of the brain it may constitute up to 2% of the total protein content. Activation of CaM kinase II has been linked to memory and learning processes in the vertebrate nervous system. CaM Kinase II is a complex of about 12 subunits that exist in four differentially expressed forms (α, β, γ, and δ). In the inactive state there is a strong interaction between the inhibitory and catalytic domains of the enzyme. The binding of Ca^{2+}/CaM allows the catalytic domain to phosphorylate the inhibitory domain. Once activated, CaM Kinase II retains significant activity even after the withdrawal of Ca^{2+}, thereby prolonging the duration of kinase activity. Several synthetic and naturally occurring compounds have been shown to bind CaM in a Ca^{2+}-dependent manner and block the activation of CaM-dependent enzymes. These compounds have been extensively used in investigating the mechanism of Ca^{2+}-binding and activation in biological systems.

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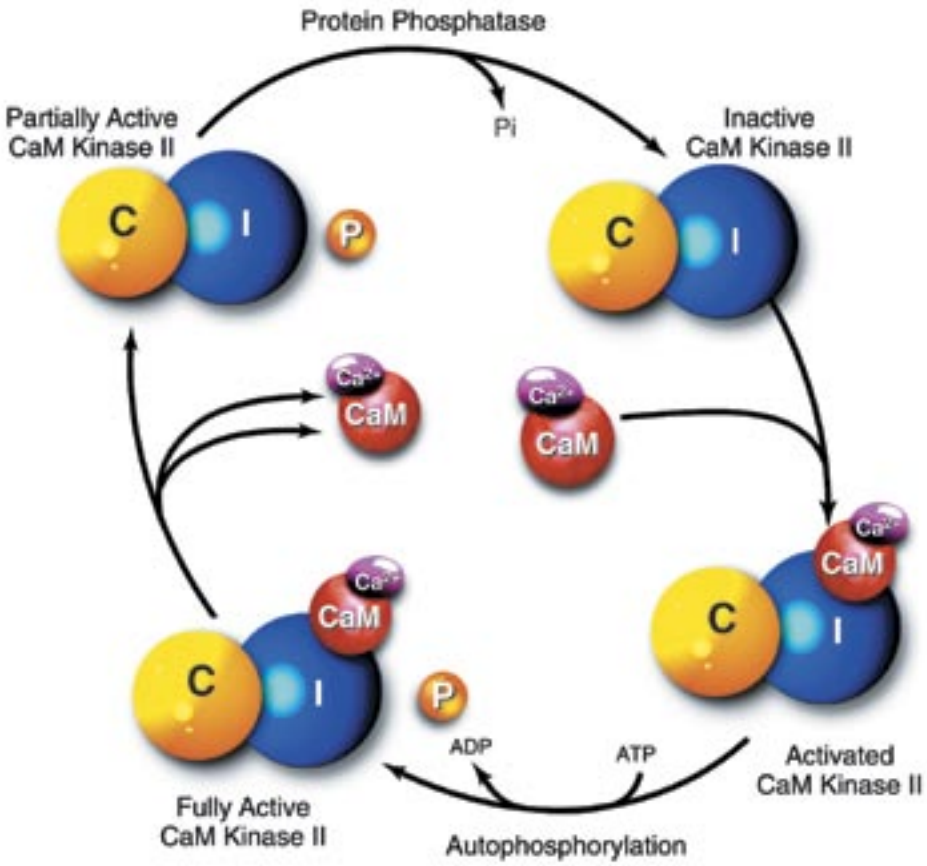

Calmodulin–Dependent Protein Kinase (CaM Kinase Inhibitors)

Product	Cat. No.	Comments	Size
Autocamtide-2 Related Inhibitory Peptide (AIP)	**189480**	Non-phosphorylatable analog of Autocamtide-2 (Cat. No. 189475) that is a highly specific and potent inhibitor of CaM kinase II (IC_{50} = 40 nM).	500 µg
Autocamtide-2 Related Inhibitory Peptide II	**189484**	An AIP-related peptide where Ala^3 and Val^{10} are replaced with Lys and Phe. Highly specific and potent inhibitor of CaM kinase II (IC_{50} = 4.1 nM).	1 mg
Autocamtide-2 Related Inhibitory Peptide II, Cell-Permeable	**189485**	A highly specific, potent, cell-permeable inhibitor of CaM kinase II. Contains the Antennapedia transport peptide sequence fused to the N-terminus of AIP-II (Cat. No. 189484).	1 mg
Autocamtide-2 Related Inhibitory Peptide, Myristoylated	**189482**	This peptide corresponds to AIP (Cat. No. 189480) which has been myristoylated at the N-terminus, enhancing its cell-permeability.	500 µg
Calmodulin-Binding Domain	**208734**	A potent calmodulin antagonist that inhibits the activation of CaM kinase II (IC_{50} = 52 nM).	1 mg
Ca^{2+}/Calmodulin Kinase II Inhibitor, 281-309	**208711**	A synthetic peptide containing the CaM-binding domain (290-309) and the autophosphorylation site (Thr^{286}) of CaM kinase II. Inhibits CaM kinase II by blocking Ca^{2+}/calmodulin activation (IC_{50} = 80 nM) and enzyme-active site (IC_{50} = 2 µM).	500 µg
[Ala^{286}]-Ca^{2+}/Calmodulin Kinase II Inhibitor, 281-301	**208710**	A synthetic peptide corresponding to residues 281-301 of the α subunit of CaM kinase II that acts as a potent inhibitor (IC_{50} = 2 µM) of CaM kinase II catalytic fragment. Inhibition is competitive with respect to ATP and in a noncompetitive manner with respect to peptide substrate.	500 µg
Calmodulin Kinase IINtide	**208920**	A potent and specific inhibitor of CaM Kinase II (IC_{50} = 50 nM). Does not affect the activity of CaM Kinase I, IV, CaM KK, PKA or PKC.	1 mg
Calmodulin Kinase IINtide, Myristoylated	**208921**	The myristoylated, cell–permeable form of CaM Kinase IINtide (Cat. No. 208920).	1 mg
H-89, Dihydrochloride	**371963**	A cell-permeable selective and potent inhibitor of protein kinase A (K_i = 48 nM). Inhibits other kinases at higher concentrations: MLCK (K_i = 28.3 µM), CaM kinase II (K_i = 29.7 µM), PKC (K_i = 31.7 µM), casein kinase I (K_i = 38.3 µM), and Rho Kinase II (IC_{50} = 270 nM).	1 mg
HA 1004, Dihydrochloride	**371964**	An inhibitor of CaM kinase II (K_i = 13 µM), MLCK (K_i = 150 µM), PKA (K_i = 2.3 µM), PKC (K_i = 40 µM), and PKG (K_i = 1.3 µM).	1 mg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable inhibitor of CaM kinase II (K_i = 1.8 nM), MLCK (K_i = 17 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), and protein kinase G (K_i = 20 nM).	100 µg
K-252a, *Nocardiopsis* sp. in Solution	**420297**	A cell-permeable inhibitor of CaM kinase II (K_i = 1.8 nM), MLCK (K_i = 17 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), and protein kinase G (K_i = 20 nM).	100 µg
KN-62	**422706**	A cell-permeable, selective inhibitor of CaM kinase II (K_i = 900 nM) that binds directly to the CaM-binding site of the enzyme.	1 mg
KN-92	**422709**	Useful as a negative control for KN-93 (Cat. No. 422708), a CaM kinase II inhibitor.	1 mg
KN-93	**422708**	Cell-permeable, competitive inhibitor of rat brain CaM kinase II (K_i = 370 nM). Selectively binds to the CaM-binding site of the enzyme and prevents the association of CaM with CaM Kinase II.	1 mg 5 mg
KN-93 in Solution	**422712**	Cell-permeable, competitive inhibitor of rat brain CaM kinase II (K_i = 370 nM). Selectively binds to the CaM-binding site of the enzyme and prevents the association of CaM with CaM Kinase II.	1 mg
KN-93, Water-Soluble	**422711**	A water-soluble form of the CaM kinase II inhibitor KN-93 (Cat. No. 422708).	1 mg
Lavendustin C	**234450**	Potent inhibitor of CaM Kinase II (IC_{50} = 200 nM) and $pp60^{c\text{-}src}$ (IC_{50} = 200 nM).	1 mg
STO-609	**570250**	A cell-permeable, highly selective, potent, ATP-competitive inhibitor of CaM kinase kinase (CaM-KK) (IC_{50} = 320 nM and 106 nM for CaM-KKα and CaM-KKβ isoforms, respectively). Binds to the catalytic domain of CaM-KK, and inhibits autophosphorylation. Does not significantly affect the activities of CaM-KII, MLCK (IC_{50} ~27 µM), CaM-KI, CaM-KIV, PKA, PKC and p42 MAP kinase (IC_{50} >27 µM).	5 mg

Casein Kinase (CK) Inhibitors

Casein kinases I and II (CKI and CKII) are highly conserved, ubiquitous serine/threonine protein kinases that play a significant role in neoplasia and cell survival. CKI can be found in the nucleus and the cytosol and is bound to the cytoskeleton and membranes. The CKI family consists of several isoforms (CKIα, β, γ1, γ2, γ3, δ, and ε) encoded by seven distinct genes. It plays a significant role in the regulation of circadian rhythm, intracellular trafficking and also acts as a regulator of Wnt signaling, nuclear import, and the progression of Alzheimer's disease. CKII has traditionally been classified as a messenger-independent protein serine/threonine kinase and consists of two catalytic and two regulatory subunits. It plays an important role in the progression of the cell cycle and in maintenance of cell viability. It is highly conserved and is known to phosphorylate about 300 different proteins. CKII activity is required at transition points of the cell cycle. Excessive activity of CKII has been linked to oncogenic transformation and the development of primary and metastatic tumors.

Casein Kinase Inhibitors

Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	A shorter alkyl chain derivative of W-7 (Cat. No. 681629) that inhibits CKI (K_i = 80 μM), CKII (K_i = 5.1 μM), MLCK (K_i = 7.4 μM), PKA (K_i = 4.3 μM), PKC (K_i = 47 μM) and PKG (K_i = 3.8 μM).	10 mg
Casein Kinase II Inhibitor	**218697**	A cell-permeable benzotriazolo compound that acts as a highly selective, ATP/GTP-competitive CKII inhibitor (IC_{50} = 900 nM and 1.6 μM for rat liver and human recombinant CKII, respectively) and DYRK (IC_{50} <1 μM for DYRK1a).	10 mg
5,6-Dichloro-1-β-D-ribo-furanosylbenzimidazole (DRB)	**287891**	Potent and specific inhibitor of casein kinase II (IC_{50} = 6 μM).	50 mg
H-89, Dihydrochloride	**371963**	A cell-permeable selective and potent inhibitor of PKA (K_i = 48 nM). At higher concentrations it also inhibits MLCK (K_i = 28.3 μM), CaM kinase II (K_i = 29.7 μM), PKC (K_i = 31.7 μM), CKI I (K_i = 38.3 μM), and Rho kinase II (IC_{50} = 270 nM).	1 mg
Hypericin	**400076**	A potent inhibitor of CKII (IC_{50} = 6 nM). Also inhibits the activity of PKC (IC_{50} = 3.3 μM), MAP kinase (IC_{50} = 4 nM), and the protein tyrosine kinase activity of the insulin receptor (IC_{50} = 20 - 29 nM) and the EGF receptor (IC_{50} = 35 nM).	1 mg
IC261	**400090**	A potent and selective inhibitor of CKIδ (IC_{50} = 0.7 - 1.3 μM) and CK1ε (IC_{50} = 0.6 - 1.4 μM). Also inhibits CK1α_1 at much higher concentrations (IC_{50} = 11 - 21 μM). The inhibition is competitive with respect to ATP.	5 mg

Key: CKI-Casein kinase I; CKII-Casein kinase II; MLCK-myosin light chain kinase; PKA-Protein kinase A; PKC-Protein kinase C

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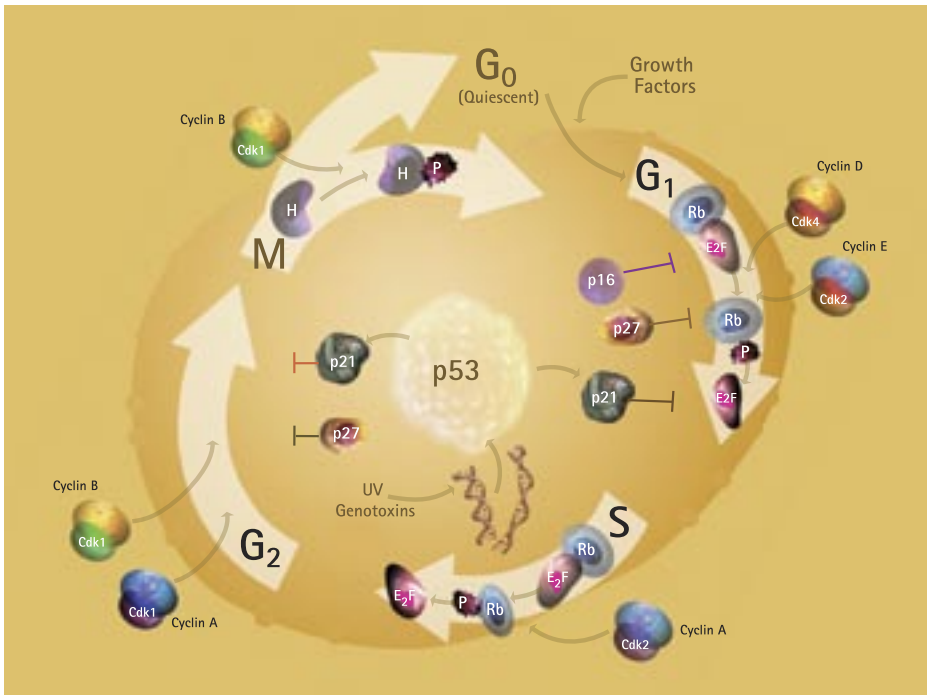
Cyclin-Dependent Kinase (Cdk) Inhibitors

Cell cycle progression is regulated by a series of sequential events that include the activation and subsequent inactivation of cyclin dependent kinases (Cdks) and cyclins. Cdks are a group of serine/threonine kinases that form active heterodimeric complexes by binding to their regulatory subunits, cyclins. Several Cdks, mainly Cdk2, Cdk4, and Cdk6, work cooperatively to drive cells from G_1 phase into S phase. Cdk4 and Cdk6 are involved in early G_1 phase, whereas Cdk2 is required to complete G_1 phase and initiate S phase. Both Cdk4 and Cdk6 form active complexes with the D type of cyclins (cyclins D1, D2, and D3). Cdk2 is sequentially activated by the E type of cyclins, cyclins E1 and E2, during G_1/S transition stage. A type cyclins, cyclin A1 and A2, play a role during the S phase. Cdk2/cyclin A complex appears during the late S phase and plays a role in progression of DNA replication. The cyclins that are involved in regulating the passage of the cell from the G_2 checkpoint into M phase are known as mitotic cyclins and they associate with mitotic Cdks. Similarly, cyclins that are involved in the passage of cells from the G_1 checkpoint into S phase are called G_1 cyclins. Once the Cdks have completed their role, they undergo a rapid programmed proteolysis via ubiquitin-mediated delivery to the proteasome complex.

It is important to note here that Cdk5, a serine-threonine kinase, originally cloned from HeLa cells, is not directly involved in cell cycle. It is primarily active in neuronal tissue. Cdk5, in conjunction with its neuron-specific activator p35 (Cdk5/p35), has been implicated in tau hyperphosphorylation. Cdk5/p35 is also involved in neuronal migration and differentiation during development of the nervous system.

The enzymatic activity of a Cdk is regulated at three levels: cyclin association, subunit phosphorylation, and association with Cdk inhibitors. When cyclins initially bind to Cdks, the resulting complex is inactive. The phosphorylation of Cdks by Cdk activating kinases leads to their activation. Two main categories of Cdk inhibitors are reported in cells. They are the INK and the WAF/Kip families. The members of the INK family, INK4A (p16), INK4B (p15), INK4C (p18), and INK4D (p19), bind to Cdk4 and Cdk6 and block their interaction with D type cyclins thereby inhibiting Cdk activity. The members of the WAF/Kip family, WAF1 (p21), Kip1 (p27), and Kip2 (p57), form heterotrimeric complexes with the G_1/S Cdks. Their major action is reported to be the inhibition of the kinase activity of Cdk/cyclin E complex.

From a therapeutic standpoint Cdks are considered promising targets in cancer chemotherapy. The most promising strategies involve designing inhibitors that either block Cdk activity or prevent their interaction with cyclins. Most of the currently available molecules target the ATP-binding site of these enzymes. Such an approach might create serious problems as catalytic residues are well conserved across eukaryotic protein kinases. However, compounds such as Flavopiridol, Olomoucine, and Butyrolactone-1 that exhibit greater specificity for Cdks have shown promise.



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Cyclin-Dependent Kinase (Cdk) Inhibitors

Product	Cat. No.	Comments	Size
Alsterpaullone	**126870**	A potent inhibitor of Cdk1/cyclin B (IC_{50} = 35 nM). Also inhibits the activity of Cdk5/p25-dependent phosphorylation of DARPP-32. One of the most active paullones that acts by competing with ATP for binding to GSK-3β and inhibits the phosphorylation of tau.	1 mg
Aloisine A	**128125**	A potent, selective, reversible, and ATP-competitive inhibitor of Cdks (IC_{50} = 150 nM for Cdk1/cyclin B, 120 nM for Cdk2/cyclin A, 400 nM for Cdk2/cyclin E, and 160 nM for Cdk5/p35). Also inhibits GSK-3 (IC_{50} = 500 nM for GSK-3α and 1.5 μM for GSK-3β), JNK (IC_{50} ~3 - 10 μM), ERKs (IC_{50} = 18 μM for ERDK and 22 μM for ERK2), PIM1 (IC_{50} >10 μM), and insulin receptor tyrosine kinase (IC_{50} = 60 μM).	5 mg
Aloisine, RP106	**128135**	A cell-permeable, pyrrolo-pyrazine compound that acts as a potent, selective ATP-competitive inhibitor of Cdk1/cyclin B (IC_{50} = 700 nM), Cdk5/p25 (IC_{50} = 1.5 μM), and GSK-3 (IC_{50} = 920 nM).	5 mg
Bohemine	**203600**	A synthetic, cell-permeable, Cdk inhibitor (IC_{50} = 1 μM) that is structurally similar to Olomoucine (Cat. No. 495620) and Roscovitine (Cat. No. 495620).	1 mg 5 mg
Cdk Inhibitor, p35	**219457**	An analog of Olomoucine (Cat. No. 495620) that acts as a potent inhibitor of Cdk1 (IC_{50} = 100 nM) and Cdk2 (IC_{50} = 80 nM).	1 mg
Cdk1 Inhibitor	**217695**	A selective, ATP-competitive inhibitor of Cdk1/cyclin B (IC_{50} = 5.8 μM for Cdk1 and 25 μM for Cdk5). Does not affect the activity of GSK-3β even at 100 μM concentrations. Binds to the ATP pocket in the Cdk1 active site.	5 mg
Cdk1 Inhibitor, CGP74514A	**217696**	A cell-permeable, potent, and selective inhibitor of Cdk1/cyclin B (IC_{50} = 25 nM).	5 mg
Cdk1 Inhibitor III	**217697**	A cell-permeable and selective inhibitor of Cdk1/cyclin B (IC_{50} = 28.8 μM).	1 mg 5 mg
Cdk1/5 Inhibitor	**217720**	A selective and potent inhibitor of Cdk1 and Cdk5 (IC_{50} = 600 nM for Cdk1/cyclin B and 400 nM for Cdk5/p25 respectively).	5 mg
Cdk2 Inhibitor I	**219442**	A potent inhibitor of Cdk2 (K_d = 38 nM).	1 mg
Cdk2 Inhibitor II	**219445**	A potent and selective inhibitor of Cdk2 (IC_{50} = 60 nM).	1 mg 5 mg
Cdk2 Inhibitor III	**238803**	A cell-permeable, selective, reversible, ATP-competitive inhibitor of Cdk2/cyclin A and Cdk2/cyclin E (IC_{50} = 500 nM).	1 mg 5 mg
Cdk2/5 Inhibitor	**219448**	An aminopyrimidine derivative that acts as a selective inhibitor of Cdk2/cyclin E and Cdk5/p25 (K_i = 2 μM). The inhibition is competitive with respect to ATP.	5 mg
Cdk2/Cyclin Inhibitory Peptide I	**238801**	A cell-permeable peptide inhibitor derived from the consensus sequence, PVKRRLFG, that serves as the docking site for Cdk2/cyclin complexes. Blocks the phosphorylation of substrates by Cdk2/cyclin A and Cdk2/cyclin E complexes.	500 μg
Cdk2/Cyclin Inhibitory Peptide II	**238802**	A cell-permeable peptide inhibitor derived from the cell-cycle regulatory transcription factor, E2F, that is derived from the Cdk2/cyclin A binding motif. Blocks the phosphorylation of substrates by Cdk2/cyclin A and Cdk2/cyclin E complexes.	500 μg
NEW Cdk4 Inhibitor	**219476**	A cell-permeable, potent, selective ATP-competitive inhibitor of Cdk4/cyclin D1 (IC_{50} = 76 nM).	1 mg
Compound 52	**234503**	A potent, cell-permeable, and selective inhibitor of the cell cycle-regulating kinase Cdc28p (IC_{50} = 7 μM) and the related Pho85p kinase (IC_{50} = 2 μM).	1 mg
Fascaplysin, Synthetic	**341251**	A cell-permeable, potent, ATP-competitive inhibitor of Cdk4/cyclin D1 (IC_{50} = 350 nM).	1 mg
Hymenialdisine, *Stylissa damicornis*	**400085**	A cell-permeable, ATP-competitive inhibitor of MEK-1 (IC_{50} = 6 nM), Cdk1/cyclin B (IC_{50} = 22 nM); Cdk2/cyclin E (IC_{50} = 40 nM); Cdk5/p35 (IC_{50} = 28 nM); and GSK-3β (IC_{50} = 10 nM).	
Indirubin-3′-monoxime	**402085**	A potent cell-permeable inhibitor of GSK-3β (IC_{50} = 22 nM) and Cdks (IC_{50} = 180 nM for Cdk1 and 100 nM for Cdk5).	1 mg
Indirubin-3′-monoxime, 5-Iodo-	**402086**	A highly potent, cell-permeable inhibitor of GSK-3β (IC_{50} = 9 nM) and Cdk1 (IC_{50} = 25 nM) and Cdk5 (IC_{50} = 20 nM). Inhibition is competitive with respect to ATP.	1 mg
Indirubin-3′-monoxime-5-sulfonic Acid	**402088**	A potent and selective inhibitor of Cdk1 and Cdk5 (IC_{50} = 5 nM for Cdk1; IC_{50} = 7 nM for Cdk5). Inhibition is competitive with respect to ATP. Also acts as a potent inhibitor of GSK-3β (IC_{50} = 80 nM).	1 mg

Cyclin-Dependent Kinase (Cdk) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Kenpaullone	**422000**	A potent, cell-permeable, ATP-competitive inhibitor of GSK-3β (IC_{50} = 230 nM), Lck (IC_{50} = 470 nM) and Cdks. Inhibits Cdk1/cyclin B (IC_{50} = 400 nM, Cdk2/cyclin A (IC_{50} = 680 nM), Cdk2/cyclin E (IC_{50} = 7.5 μM), Cdk5/p25 (IC_{50} = 850 nM). Also Inhibits c-Src (IC_{50} = 15 μM), casein kinase II (IC_{50} = 20 μM), ERK1 (IC_{50} = 20 μM), and ERK2 (IC_{50} = 9 μM) at higher concentrations.	1 mg
Olomoucine	**495620**	A potent, selective, ATP-competitive inhibitor of $p34^{cdc2}$/cyclin B (IC_{50} = 7 μM) and related kinases, including $p33^{cdk2}$/cyclin A (IC_{50} = 7 μM), $p33^{cdk2}$/cyclin E (IC_{50} = 7 μM), $p33^{cdk5}$/p35 (IC_{50} = 3 μM), and $p44^{MAPK}$ (IC_{50} = 25 μM).	1 mg 5 mg
NEW Olomoucine II	**495621**	A cell-permeable, potent, ATP-competitive inhibitor of Cdk1/cyclin B (IC_{50} = 20 nM).	5 mg
Olomoucine, Iso-	**495622**	A negative control compound for studies involving Olomoucine (Cat. No. 495620) (IC_{50} > 500 μM for $p34^{cdc2}$/cyclin B; IC_{50} >1 mM for $p33^{cdk5}$/p35; IC_{50} >1 mM for $p34^{cdk4}$/cyclin D).	1 mg 5 mg
Olomoucine, N^9-Iso-propyl-	**495623**	A Cdc2 kinase inhibitor (IC_{50} = 2 μM) that is more potent than Olomoucine (Cat. No. 495620).	5 mg
Protein Kinase Inhibitor, DMAP	**476493**	A puromycin analog that acts as a protein kinase inhibitor. Also inhibits $p34^{cdc2}$/cyclin B (IC_{50} = 300 μM).	50 mg
Purvalanol A	**540500**	A potent, cell-permeable, and selective inhibitor of Cdks (IC_{50} = 4 nM for Cdc2/cyclin B; 70 nM for Cdk2/cyclin A; 35 nM for Cdk2/cyclin E; and 75 nM for Cdk5/p35).	1 mg
Roscovitine	**557360**	A potent, selective, ATP-competitive inhibitor of Cdks. Inhibits $p34^{cdc2}$/cyclin B (IC_{50} = 650 nM), $p33^{cdk2}$/cyclin A (IC_{50} = 700 nM), $p33^{cdk2}$/cyclin E (IC_{50} = 700 nM), and $p33^{cdk2}$/p35 (IC_{50} = 200 nM).	1 mg 5 mg
Roscovitine, Immobilized	**557361**	An immobilized form of Roscovitine (Cat. No. 557360) that is covalently attached to hydrophilic acrylic beads via a 3-carbon spacer. Useful to affinity-precipitate Cdks and other functionally related proteins from cell or tissue extracts. Note: 1 set = 25 mg of Roscovitine Immobilized beads and 25 mg of control beads.	1 Set
Roscovitine, (S)-Isomer	**557362**	The (S)-enantiomer of Roscovitine (Cat. No. 557360). Potently inhibits $p34^{cdc2}$/cyclin B kinase (IC_{50} = 800 nM).	1 mg
SU9516	**572650**	A cell-permeable, potent, and selective ATP-competitive inhibitor of Cdks (IC_{50} = 22 nM for Cdk2/cyclin A; 40 nM for Cdk1/cyclin B; and 200 nM for Cdk4/cyclin D1).	5 mg
WHI-P180, Hydrochloride	**681500**	An ATP-competitive inhibitor of Cdk2 (IC_{50} = 1 μM).	500 μg 1 mg

ProteoEnrich™ ATP-Binders™ Kit

For group separation of protein kinases and other ATP-binding proeins, yielding partially purified cell extracts enriched in protein kinases that retain enzymatic activity. This kit is based on an affinity resin containing immobilized ATP. Compatible with 2D gel electrophoresis, SDS-Page/tandem mass spectrometry, Western blot analysis, and activity assays. The kit provides sufficient reagents to perform enrichment from up to 17.5 mg crude protein.

Cat. No. 71438-3 **1 kit**

DNA-Dependent Protein Kinase (DNA-PK) Inhibitors

DNA-dependent protein kinase (DNA-PK) is a serine/threonine kinase composed of a large catalytic subunit and two DNA-binding subunits, Ku70 and Ku80. The catalytic subunit is inactive by itself and requires DNA-binding subunits to direct it to DNA and trigger kinase activity. DNA-PK phosphorylates protein targets and also undergoes auto-phosphorylation. The auto-phosphorylation activity has been shown to be essential for repair of random double-strand breaks. DNA-PK phosphorylates p53 on Ser^{15} and Ser^{37}. Phosphorylation of Ser^{15} is suggested to be essential for p53 function. Ser^{15} resides within the critical N-terminal region of p53, which controls the interaction of p53 with the transcriptional apparatus and with the MDM-2 protein. Phosphorylation of Ser^{15} weakens the association of p53 with MDM-2 and inhibits the repression of p53 by MDM-2. Phosphorylation of Thr^{18} of p53 by casein kinase 1 (CK1) or CK1-like activity, stimulated by Phosphorylation of Ser^{15}, is believed to be a contributing factor for the inhibition of p53 binding by MDM-2. Phosphorylation of DNA-PK by the PKC_{δ} catalytic fragment is also shown to cause the dissociation of DNA-PK from DNA, resulting in its inactivation. Cells defective in DNA-PK components are reported to be hypersensitive to killing by ionizing radiation owing to their inability to repair double-stranded breaks effectively.

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DNA-Dependent Protein Kinase (DNA-PK) Inhibitors

Product	Cat. No.	Comments	Size
NEW DNA-PK Inhibitor	**260960**	A cell-permeable vanillin derivative that acts as a potent and selective inhibitor of DNA-PK (IC_{50} = 15 μM) and DNA-PK-mediated double strand break.	10 mg
NEW DNA-PK Inhibitor II	**260961**	A cell-permeable, potent, specific, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 230 nM). It is highly selective towards DNA-PK over other PI 3-kinase related enzymes (IC_{50} = 13 μM for PI 3-kinase and >100 μM for ATM and ATR).	5 mg

Glycogen Synthase Kinase (GSK) Inhibitors

Glycogen Synthase Kinase-3 (GSK-3; tau protein kinase I), a highly conserved, ubiquitously expressed serine/threonine protein kinase, is involved in the signal transduction cascades of multiple cellular processes. It is negatively regulated by protein kinase B/Akt and by the Wnt signaling pathway. GSK-3 exists in two functionally distinct forms, a 51 kDa GSK-3α and a 47 kDa GSK-3β. Dysregulated GSK-3 has been implicated in the development of diabetes, cancer, and Alzheimers's disease. Elevated levels of GSK-3β have been shown in pre-tangle and in phosphorylated tau bearing neurons. GSK-3β accounts for phosphorylation of most major sites of fetal and paired helical filament-tau. β-Amyloid peptides are also shown to activate GSK-3β, suggesting that activation of GSK-3β is a key mechanism in the pathogenesis of Alzheimer's disease. GSK-3 inhibitors hold considerable promise for reducing tau phosphorylation and debilitating effects of Alzheimer's disease.

Glycogen Synthase Kinase Inhibitors

Product	Cat. No.	Comments	Size
Aloisine A	**128125**	An inhibitor of GSK-3 (IC_{50} = 500 nM for GSK-3α and 1.5 μM for GSK-3β). Also acts as a potent, selective, reversible, and ATP-competitive inhibitor of Cdks (IC_{50} = 150 nM for Cdk1/cyclin B, 120 nM for Cdk2/cyclin A, 400 nM for Cdk2/cyclin E, and 160 nM for Cdk5/p35).	5 mg
Aloisine, RP106	**128135**	A cell-permeable, potent, selective ATP-competitive inhibitor of Cdk1/cyclin B (IC_{50} = 700 nM), Cdk5/p25 (IC_{50} = 1.5 μM), and GSK-3 (IC_{50} = 920 nM).	5 mg
FRATtide	**344265**	A peptide corresponding to amino acids 188 - 226 of FRAT1 (frequently rearranged in advanced T-cell lymphomas 1), a mammalian homolog of GSK-3 binding protein. Binds to the C-terminal lobe of GSK-3 and prevents the binding of "unprimed" substrates such as axin, β-catenin and tau. Exhibits little effect on GSK-3 catalyzed phosphorylation of "primed" (pre-phosphorylated) substrates such as glycogen synthase and eIF2B.	500 μg
GSK-3β Inhibitor I	**361540**	A thiadiazolidinone (TDZD) analog that acts as a highly selective, non-ATP competitive inhibitor of GSK-3β (IC_{50} = 2 μM). Proposed to bind to the active site of GSK-3β.	5 mg
GSK-3β Inhibitor II	**361541**	A 2-thio-[1,3,4]-oxadiazole-pyridyl derivative that acts as a potent inhibitor of GSK-3β (IC_{50} = 390 nM).	5 mg
GSK-3β Inhibitor III	**361542**	An oxothiadiazolidine-3-thione analog that acts as a non-ATP competitive inhibitor of GSK-3β (IC_{50} = 10 μM).	1 mg
NEW GSK-3β Inhibitor VII	**361548**	A cell-permeable, selective, irreversible, and non-ATP competitive inhibitor of GSK-3β (IC_{50} = 500 nM).	5 mg
NEW GSK-3β Inhibitor VIII	**361549**	A cell-permeable, potent, and highly specific inhibitor of glycogen synthase kinase-3β (GSK-3β) (IC_{50} = 104 nM). Inhibition is competitive with respect to ATP (K_i = 38 nM).	5 mg
NEW GSK-3β Inhibitor IX	**361550**	A cell-permeable, highly potent, selective, reversible, and ATP-competitive inhibitor of GSK-3α/β (IC_{50} = 5 nM). At higher concentrations, inhibits Cdk2/cyclin A (IC_{50} = 300 nM) and Cdk5/p25 (IC_{50} = 83 nM).	1 mg
GSK-3β Peptide Inhibitor	**361545**	A phosphorylated peptide that acts as a substrate-specific, competitive inhibitor of GSK-3β (IC_{50} = 150 μM). Inhibits Cdc2, CK II, MAPK, PKA, PKB, and PKCδ at higher concentrations (200 μM results in 85 - 100% inhibition).	1 mg
GSK-3β Peptide Inhibitor, Cell-Permeable	**361546**	A cell-permeable, myristoylated form of GSK-3β Peptide Inhibitor (Cat. No. 361545) with a glycine spacer. Acts as a selective, substrate-specific, competitive inhibitor of GSK-3β (IC_{50} = 40 μM). Does not affect the activities of Cdc2, PKB, or PKC.	1 mg
Hymenialdisine, *Stylissa damicornis*	**400085**	A potent, ATP-competitive inhibitor of GSK-3β (IC_{50} = 10 nM). Also inhibits several other protein kinases, including MEK-1 (IC_{50} = 6 nM), Cdks (IC_{50} = 22 nM for Cdk1/cyclin B, 40 nM for Cdk2/cyclin E, and 28 nM for Cdk5/p35), and casein kinase 1 (IC_{50} = 35 nM).	500 μg
Indirubin-3′-monoxime	**402085**	A potent cell-permeable inhibitor of GSK-3β (IC_{50} = 190 nM) and cyclin-dependent kinases (IC_{50} = 180 nM for Cdk1).	1 mg
Indirubin-3′-monoxime, 5-Iodo-	**402086**	A highly potent, cell-permeable inhibitor of GSK-3β (IC_{50} = 9 nM). Reported to inhibit GSK-3β phosphorylation of human tau protein *in vitro* (IC_{50} ~100 nM) and in cells (effective concentration = 20 μM). Also inhibits Cdk1 (IC_{50} = 25 nM) and Cdk5 (IC_{50} = 20 nM).	1 mg
Indirubin-3′-monoxime-5-sulfonic Acid	**402088**	A highly potent, selective, ATP competitive inhibitor of Cdks 1 and 5 (IC_{50} = 5 nM for Cdk1; IC_{50} = 7 nM for Cdk5). Also acts as a potent inhibitor of GSK-3β (IC_{50} = 80 nM).	1 mg
Kenpaullone	**422000**	A potent, cell-permeable, ATP competitive inhibitor of GSK-3β (IC_{50} = 230 nM), Lck (IC_{50} = 470 nM) and Cdks. Inhibits Cdk1/cyclin B (IC_{50} = 400 nM), CdK2/cyclin A (IC_{50} = 680 nM), Cdk2/cyclin E (IC_{50} = 7.5 μM), and Cdk5/p25 (IC_{50} = 850 nM).	1 mg

c-Jun N-Terminal Kinase (JNK/SAP Kinase) Inhibitors *(see other MAP Kinase Inhibitors, pg. 13)*

Jun N-terminal kinase (JNK), a serine-directed protein kinase, is involved in the phosphorylation and activation of c-Jun and ATF2 and plays a significant role in metabolism, growth, cell differentiation, and apoptosis. The three isoforms of JNK known as JNK1, 2 and 3 are encoded by 3 independent genes. JNK1 and 2 exhibit broad tissue expression profiles. In contrast, JNK3 is expressed predominantly in the central nervous system. JNK is activated in response to inflammation and endotoxins and its activation can mediate pro-inflammatory gene expression.

Jun N-Terminal Kinase (JNK SAP Kinase) Inhibitors

Product	Cat. No.	Comments	Size
Dicoumarol	**287897**	A quinone reductase inhibitor that competes with NADH or NADPH for binding to the oxidized form of NAD(P)H:quinone oxidoreductase (NQO1). Shown to inhibit IGF-I-, menadione-, and DMNQ-mediated activation of stress-activated protein kinase/SAPK/JNK and subsequent phosphorylation of c-Jun, as well as stress-induced activation of SAPK/JNK. Does not affect the phosphorylation of p38 or Akt (protein kinase B).	500 mg
JNK Inhibitor I, (L)-Form, Cell-Permeable [(L)-HIV-TAT$_{48-57}$PP-JBD$_{20}$]	**420116**	A cell-permeable, biologically active peptide consisting of a carboxyl- terminal sequence derived from the JNK-binding domain (JBD) and an amino-terminal peptide containing the HIV-TAT$_{48-57}$ sequence that imparts cell-permeability. Blocks the activation domain of JNK and prevents the activation of c-Jun (IC_{50} ~1 μM). Inhibits IL-1β-induced c-Jun and c-fos expression in insulin secreting βTC-3 cells and offers protection against apoptosis. Does not affect the activities of ERK1, ERK2, or p38 in any significant manner.	1 mg
JNK Inhibitor I, (L)-Form, Cell-Permeable, Negative Control (GRKKRRQRRRPP-NH_2)	**420118**	A highly cell-permeable carrier decapeptide derived from HIV-TAT$_{48-57}$ sequence that is modified with two proline residues. Serves as a useful negative control for studies involving JNK Inhibitor I, (L)-Form, Cell-permeable (Cat. No. 420116).	1 mg
JNK Inhibitor II (SP600125)	**420119**	A potent, cell-permeable, selective, and reversible inhibitor of JNK (IC_{50} = 40 nM for JNK-1 and JNK-2 and 90 nM for JNK-3). The inhibition is competitive with respect to ATP. Exhibits over 300-fold greater selectivity for JNK as compared to ERK1 and p38-2 MAP kinases.	5 mg
JNK Inhibitor II, Negative Control (N^1-Methyl-1,9,-pyrazolo-anthrone)	**420123**	A useful negative control for JNK Inhibitor II (SP600125, Cat. No. 420119). Inhibits JNK2 and JNK3 only at much higher concentrations (IC_{50} = 18 μM and 24 μM, respectively) compared to JNK Inhibitor II (IC_{50} = 40 and 90 nM, respectively).	1 mg
JNK Inhibitor III, Cell-Permeable (HIV-TAT$_{47-57}$-gaba-c-Junδ$_{33-57}$)	**420130**	A cell-permeable peptide constructed by fusing the JNK binding domain sequence (δ) (amino acids 33 - 57) of human c-Jun to the HIV-TAT transduction domain sequence (amino acids 47 - 57) with a γ-aminobutyric acid (GABA) spacer. Disrupts c-Jun/JNK complex formation and subsequent phosphorylation and activation of c-Jun by JNK *in vitro* and in intact cells. Mode of inhibition is distinct from that of JNK Inhibitor II (SP600125; Cat. No. 420119).	1 mg
JNK Inhibitor III, Cell-Permeable, Negative Control (HIV-TAT$_{47-57}$-gaba-c-Junδ$_{33-57}$, scrambled)	**420131**	A cell-permeable peptide that contains a scrambled sequence derived from the JNK binding domain (δ) of human c-Jun (amino acids 33 - 57) fused to the HIV-TAT transduction domain (amino acids 47 - 57) via a γ-aminobutyric acid (GABA) spacer. Does not disrupt c-Jun/JNK complex formation. Serves as a negative control for JNK Inhibitor III, Cell-Permeable (Cat. No. 420130).	1 mg
NEW JNK Inhibitor IV, (D)-Form, Cell-Permeable [(D)-HIV-TAT$_{48-57}$PP-JBD$_{20}$]	**420117**	The D-*retroinverso* version of (L)-JNK Inhibitor I (420116) that readily crosses the blood-brain barrier. Competitively blocks JNK from phosphorylating many of its target substrates. Although ~15-fold less potent than (L)-JNK Inhibitor 1, it is more protease-resistant.	250 μg
Protein Kinase Inhibitor, DMAP	**476493**	A puromycin analog that acts as a protein kinase inhibitor. Reported to inhibit a number of TNF-α-induced effects, including CAP kinase activation, JNK activity, and suppression of Jun-b expression.	50 mg

Mitogen-Activated Protein (MAP) Kinase Inhibitors

The Mitogen-activated protein (MAP) kinases are a group of protein serine/threonine kinases that are activated in response to a variety of extracellular stimuli and mediate signal transduction from the cell surface to the nucleus. They regulate several physiological and pathological cellular phenomena, including inflammation, apoptotic cell death, oncogenic transformation, tumor cell invasion, and metastasis. MAP kinases, in combination with several other signaling pathways, can differentially alter the phosphorylation status of the transcription factors in a pattern unique to a given external signal. Three major types of MAP kinase cascades have been reported in mammalian cells that respond synergistically to different upstream signals. A controlled regulation of these cascades is involved in cell proliferation and differentiation, whereas unregulated activation of these MAP kinases can result in oncogenesis. The most widely studied cascade is that of ERK1/ERK2 MAP kinases. In the cell, one highly active form of ERK1 or ERK2 (dual phosphorylated) exists, which exhibits over 1000-fold greater activity than the unphosphorylated form. At any one time, there may be three low activity forms of ERKs: one unphosphorylated enzyme, and two singly phosphorylated forms that contain phosphate either at a tyrosine or a threonine residue.

The second most widely studied MAP kinase cascade is the JNK/SAPK (c-Jun kinase/stress activated protein kinase). This cascade is activated following exposure to UV radiation, heat shock, or inflammatory cytokines. The activation of these MAP kinases is mediated by Rac and cdc42, two small G-proteins. Activated cdc42 binds to PAK protein kinase and activates it. Activated PAK[65] can activate MEKK, which in turn phosphorylates SEK/JNKK and activates it. The active SEK/JNKK phosphorylates JNK/SAPK (at the TPY motif). The sites of activating phosphorylation are conserved between ERK and JNK, however, these sites are located within distinct dual specificity phosphorylation motifs (TPY for JNK and TEY for ERK).

The p38 kinase, another member of the MAP kinase family, bears similarity to the yeast MAPK Hog-1. It is activated in response to inflammatory cytokines, endotoxins, and osmotic stress. It shares about 50% homology with the ERKs. The upsteam steps in its activation of this cascade are not well defined. However, downstream activation of p38 occurs following its phosphorylation (at the TGY motif) by MKK3, a dual specificity kinase. Following its activation, p38 translocates to the nucleus and phosphoryates ATF-2. Another known target of p38 is MAPKAPK2 that is involved in the phosphorylation and activation of heat-shock proteins.

Although different MAP kinase cascades show a high degree of specificity and functional separation, some degree of cross-talk is observed between different pathways. Another important observation is that when mammalian cells are treated with mitogenic agents, ERKs are significantly activated whereas JNK/SAPK are not affected. Conversely, cells exposed to stress activate the JNK/SAPK pathway without altering the activity of ERKs. At the transcription level, even though ATF-2 is phosphorylated and activated by all three MAP kinases, and c-Jun and Elk-1 are phosphorylated by ERKs and JNK/SAPK, all these pathways result in transcriptional activity that is unique for a particular external stress.

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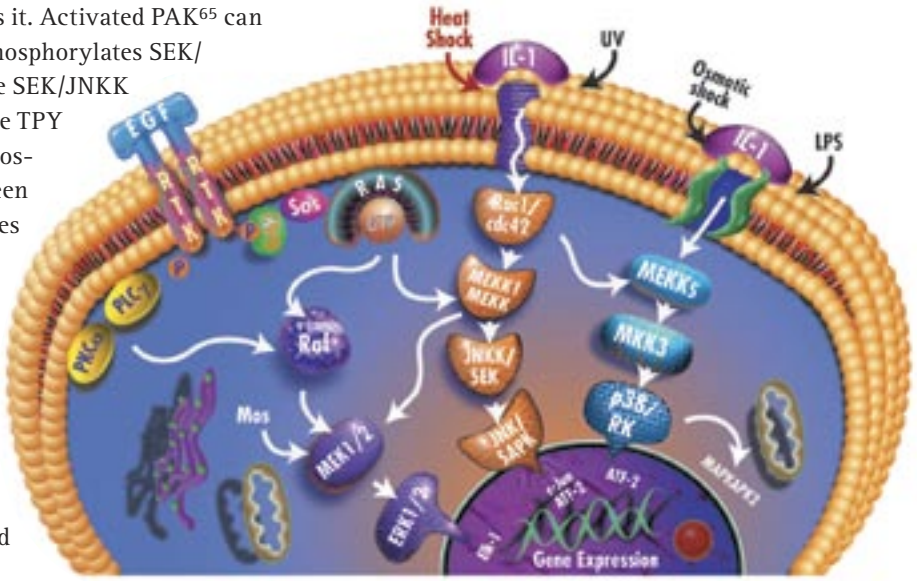

MAP Kinase Inhibitors

Product	Cat. No.	Comments	Size
AG 126	**658452**	An inhibitor of lipopolysaccaride (LPS)-induced synthesis of tumor necrosis factor-α and nitric oxide in murine peritoneal macrophages. Blocks LPS-induced tyrosine phosphorylation of a p42MAPK protein substrate.	5 mg
Anthrax Lethal Factor, Recombinant, *Bacillus anthracis*	**176900**	One of the three protein components of Anthrax toxin, lethal factor (LF) is a highly specific protease that cleaves members of the mitogen-activated protein kinase kinase (MAPKK) family. LF is comprised of four domains. Domain I binds the protective antigen to enter the target cell; domains II, III, and IV create a long groove to hold and cleave the MAPKK proteins.	100 µg
ERK Activation Inhibitor I, Cell-Permeable	**328000**	A stearated 13-amino acid peptide corresponding to the N-terminus of MEK1. Acts as a specific inhibitor of ERK activation and the transcriptional activity of Elk1. Selectively binds to ERK2 and prevents its interaction with MEK (IC_{50} = 2.5 µM).	1 mg
ERK Activation Inhibitor II, Cell-Permeable	**328005**	A 13-amino acid peptide corresponding to the N-terminus of MEK1 that is fused to the HIV-TAT membrane translocating peptide (MTP) sequence via a glycine linker. Acts as a specific inhibitor of ERK activation and the transcriptional activity of Elk1 by binding to ERK2, and prevents its interaction with MEK (IC_{50} = 210 nM).	1 mg
Hymenialdisine, *Stylissa damicornis*	**400085**	A potent, ATP-competitive inhibitor of GSK-3β (IC_{50} = 10 nM). Also inhibits several other protein kinases, including MEK-1 (IC_{50} = 6 nM), Cdks (IC_{50} = 22 nM for Cdk1/cyclin B, 40 nM for Cdk2/cyclin E, and 28 nM for Cdk5/p35), and casein kinase 1 (IC_{50} = 35 nM).	500 µg
Hsp25 Kinase Inhibitor	**385880**	A potent and selective inhibitor of mammalian heat-shock protein (Hsp25) kinase (mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2). Inhibition is competitive with respect to the substrate peptide (K_i = 8.1 µM) and non-competitively with respect to ATP (K_i = 134 µM).	1 mg
5-Iodotubercidin	**407900**	A potent inhibitor of adenosine kinase (Ki = 30 nM) and Ser/Thr-specific kinases that also acts as a potent, and competitive inhibitor of the ERK2 (K_i = 530 nM).	1 mg
MEK1/2 Inhibitor	**444939**	A cell-permeable, selective inhibitor of MEK1 (IC_{50} = 180 nM) and MEK2 (IC_{50} = 220 nM). Inhibits ERK1, MKK3/p38, MKK4, JNK, and PKC activities only at higher concentrations (IC_{50} >10 µM).	1 mg 5 mg
MEK Inhibitor II	**444938**	A cell-permeable, potent, and selective inhibitor of MEK (IC_{50} = 380 nM for MEK1).	5 mg
ML 3163	**475800**	A cell-permeable inhibitor that combines the structural features of cytokine release inhibitors SKF-86002 (Cat. No. 567305) and p38 MAP kinase inhibitor SB 203580 (Cat. No. 559389). Occupies the ATP binding site of p38 MAP kinase and inhibits its activity (IC_{50} = 4.0 µM).	1 mg
Olomoucine	**495620**	A potent and selective inhibitor of $p34^{cdc2}$/cyclin B (IC_{50} = 7 µM) and related kinases, including $p33^{cdk2}$/cyclin A (IC_{50} = 7 µM), $p33^{cdk2}$/cyclin E (IC_{50} = 7 µM), $p33^{cdk5}$/p35 (IC_{50} = 3 µM). Also acts as an inhibitor of and ERK1 (IC_{50} = 25 µM). Acts by competing for the ATP binding domain of the kinase.	1 mg 5 mg
p38 MAP Kinase Inhibitor	**506126**	A potent p38 MAP kinase inhibitor (IC_{50} = 35 nM).	500 µg
NEW p38 MAP Kinase Inhibitor III	**506121**	A cell-permeable, potent, selective, and ATP-competitive inhibitor of p38 MAP kinase (IC_{50} = 380 nM for p38α).	1 mg
PD 98059	**513000**	A potent and selective MEK inhibitor. It selectively blocks the activation of MEK, thus preventing its phosphorylation by cRaf or MEK kinase (IC_{50} = 2 – 7 µM).	5 mg
PD 169316	**513030**	A potent and selective p38 MAP kinase inhibitor (IC_{50} = 89 nM).	1 mg
SB 202190	**559388**	A potent and selective p38 MAP kinase inhibitor (IC_{50} = 50 nM for SAPK2a/p38 and 100 nM for SAPK2b/p38β2).	1 mg
SB 202190, Immobilized	**559403**	An immobilized form of the p38 MAP kinase inhibitor (Cat. No. 559388) covalently attached to hydrophilic acrylic beads via a 3-carbon spacer. Useful for affinity-precipitatation of p38 MAP kinase and other functionally related proteins from cell or tissue extracts.	1 set
SB 202190 in Solution	**559397**	A 1 mg/ml solution of SB 202190 (Cat. No. 559388) in anhydrous DMSO.	1 ml
SB 202474, Dihydrochloride	**559407**	A water-soluble form of SB 202474 (Cat. No. 559387), that serves as a negative control compound for SB 202190 (Cat. No. 559388) and SB 203580 (Cat. No. 559389) in p38 MAP kinase inhibition studies.	1 mg

MAP Kinase Inhibitor, *continued*

Product	Cat. No.	Comments	Size
SB 202474	**559387**	A negative control for MAP kinase inhibition studies.	1 mg
SB 203580	**559389**	A potent and selective p38 MAP kinase inhibitor (IC_{50} = 50 nM for SAPK2a/p38 and 500 nM for SAPK2b/p38β2).	1 mg
SB 203580 in Solution	**559398**	A 1 mg/ml solution of SB 203580 (Cat. No. 559389) in anhydrous DMSO.	1 ml
SB 203580, Iodo-	**559400**	A highly specific and potent inhibitor of p38 MAP kinase, similar to SB 203580 (Cat. No. 559389). Useful for the identification of inhibitor binding sites of p38 MAP kinase.	1 mg
SB 203580, Sulfone	**559399**	The sulfone analog of SB 203580 (Cat. No. 559389). Potently inhibits p38 MAP kinase (IC_{50} = 30 nM).	1 mg
SB 220025	**559396**	A potent and specific inhibitor of human p38 MAP kinase (IC_{50} = 60 nM). Displays 2000-fold greater selectivity for p38 MAPK over ERK (p42/p44 MAP kinase).	500 µg
SB 239063	**559404**	A potent MAP kinase inhibitor (IC_{50} = 44 nM for inhibition of recombinant purified human p38α).	500 µg
SC 68376	**565625**	A potent and selective inhibitor of p38 MAP kinase (IC_{50} = 2 – 5 µM).	1 mg
SKF-86002	**567305**	A cytokine-suppressive anti-inflammatory drug (CSAID) that acts as a specific p38 MAP kinase inhibitor. Also inhibits cyclooxygenase and 5-lipoxygenase.	5 mg
U0124	**662006**	A useful negative control for MEK inhibitors U0125 (Cat. No. 662008) and U0126 (Cat. No. 662005).	1 mg
U0125	**662008**	A potent and specific inhibitor of MEK1 and MEK2. About 10-fold less potent than U0126 (Cat. No. 662005).	1 mg
U0126	**662005**	A potent and specific inhibitor of MEK1 (IC_{50} = 72 nM) and MEK2 (IC_{50} = 58 nM).	1 mg
ZM 336372	**692000**	A potent, specific and competitive inhibitor of c-Raf (IC_{50} = 70 nM) that also inhibits p38α (IC_{50} = 2 µM) and p38β2 (IC_{50} = 2 µM).	1 mg

MAP Kinase Cascade Inhibitor Set

A set of 5 vials. Each set contains 1 mg each of FPT Inhibitor III (Cat. No. 344154) and ZM 336372 (Cat. No. 692000), 5 mg of PD 98059 (Cat. No. 513000) and 1 mg of SB 203580 (Cat. No. 559389).

Cat. No. 444185 **1 set**

MAP Kinase Inhibitor Set I

A set of 4 vials. Each set contains 5 mg of the MEK inhibitor PD 98059 (Cat. No. 513000), 1 mg each of the MAP kinase inhibitors SB 202190 (Cat. No. 559388) and SB 203580 (Cat. No. 559389), and 1 mg of the negative control, SB 202474 (Cat. No. 559387).

Cat. No. 444180 **1 set**

MAP Kinase Inhibitor Set II

A set of 4 vials. Each set contains 5 mg of PD 98059 (Cat. No. 513000), 1 mg each of SB 203580 (Cat. No. 559389), and U0126 (Cat. No. 662005), and 1 mg of the negative control, SB 202474 (Cat. No. 559387).

Cat. No. 444190 **1 set**

Myosin Light Chain Kinase (MLCK) Inhibitors

Myosin light chain kinase (MLCK), a Ca^{2+}-calmodulin dependent multi-functional enzyme, plays a critical role in the regulation of smooth muscle contraction. It regulates the contractile interaction between actin microfilaments and conventional smooth muscle and non-muscle myosin II. MLCK is composed of an N-terminal actin-binding domain, a central kinase domain, and a C-terminal myosin-binding domain. The kinase domain activates the interaction of smooth-muscle myosin with actin by phosphorylating the myosin light chain. This phosphorylation is responsible for coupling increased Ca^{2+} concentration with smooth muscle contraction. MLCK is reported to bind the actin filament in a manner that also allows the simultaneous binding of the other major thin filament components; calponin, tropomyosin, etc. The binding site is suggested to be on the outside of sub-domain 1. There is approximately one MLCK molecule for every 100 actin molecules in smooth muscle and each MLCK contains at least three of the DFRXXL motifs allowing each molecule to bind three actins (K_d = 4 μM).

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Myosin Light Chain Kinase (MLCK) Inhibitors

Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	A shorter alkyl chain derivative of W-7 (Cat. No. 681629) that inhibits MLCK (K_i = 7.4 μM), CK I (K_i = 80 μM), CK II (K_i= 5.1 μM), PKA (K_i = 4.3 μM), PKC (K_i = 47 μM) and PKG (K_i= 3.8 μM).	10 mg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable inhibitor of MLCK (K_i = 17 nM), CaM kinase II (K_i = 1.8 nM), PKC (K_i = 25 nM), and PKG (K_i = 20 nM). Also acts as a potent inhibitor (IC_{50} = 3 nM) of the protein tyrosine kinase activity of the NGF receptor gp 140trk.	100 μg
K-252a, *Nocardiopsis* sp. in Solution	**420297**	A 1 mM (100 μg/214 μl) solution of K-252a (Cat. No. 420298) in anhydrous DMSO.	100 μg
K-252b, *Nocardiopsis* sp.	**420319**	A non-selective inhibitor of MLCK (K_i = 147 nM), PKA (K_i = 90 nM), PKC (K_i = 20 nM), and PKG (K_i = 100 nM).	50 μg 100 μg
ML-7, Hydrochloride	**475880**	A cell-permeable, potent and selective inhibitor of MLCK (K_i = 300 nM). Inhibits PKA (K_i = 21 μM) and PKC (K_i = 42 μM) at much higher concentrations.	1 mg
ML-9, Hydrochloride	**475882**	A cell-permeable inhibitor of MLCK (K_i = 3.8 μM), PKA (K_i = 32 μM), and PKC (K_i = 54 μM).	1 mg
Myosin Light Chain Kinase Inhibitor Peptide 18	**475981**	A highly basic nonapeptide that acts as a selective inhibitor of MLCK (IC_{50} = 50 nM). Does not block calmodulin (CaM) or inhibit the activities of CaM Kinase II or PKA.	5 mg
Myosin Light Chain Kinase Inhibitor Peptide 480-501	**05-23-1700**	A potent inhibitor of calmodulin-dependent activation of the smooth muscle MLCK (IC_{50} = 46 nM).	500 μg 1 mg
Piceatannol	**527948**	A plant metabolite that preferentially inhibits the activity of p72Syk (IC_{50} ~10 μM). Also acts as an inhibitor of rat liver PKA catalytic subunit (cAK) (IC_{50} = 3 μM), PKC (IC_{50} = 8 μM), MLCK (IC_{50} = 12 μM).	1 mg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable broad-spectrum inhibitor of protein kinases. Inhibits MLCK (IC_{50} = 1.3 nM), CaM kinase (IC_{50} = 20 nM), PKA (IC_{50} = 7 nM), PKC (IC_{50} = 700 pM), and PKG (IC_{50} = 8.5 nM).	100 μg 250 μg

Phosphatidylinositol 3-Kinase (PI 3-Kinase) Inhibitors

The PI 3-kinases are ubiquitous, heterodimeric enzymes that play a pivotal role in the regulation of many cellular processes, including motility, proliferation and survival, and carbohydrate metabolism. They are dual-specificity enzymes capable of phosphorylating phosphoinositides. PI 3-kinases are divided into three classes. Class I kinases were the first to be characterized and include receptor-regulated heterodimeric enzymes consisting of a 110 kDa catalytic subunit and an 85 kDa regulatory subunit (p85/p110α; p85/p110β; p101/P110γ). They can use PI, PI (4)P and PI (4,5)P2 as substrates *in vitro*. The major substrate *in vivo* appears to be PI(4,5)P2. The members of this class are sensitive to wortmannin. Class II PI-3 kinases can phosphorylate PI and PI(4)P *in vitro* and show variable responses to wortmannin. This class of enzymes contains a C-2 domain at the C-terminal region that binds phospholipids in a Ca^{2+}-dependent manner. They participate in integrin signaling in platelets. Class III PI 3-kinases include Vps34 that can phosphorylate PI(3)P. The human homologue of Vps34 is reported to be sensitive to wortmannin and participates in the regulation of endocytic membrane trafficking.

Activated PI 3-kinase phosphorylates phosphoinositol (PI) substrates to produce PI(3)P, PI(3,4)P2, and PI(3,4,5)P3. These molecules act as second messengers and recruit the PI 3-K-dependent serine/threonine kinases (PDK1) and Akt from the cytoplasm to the plasma membrane. Lipid binding and membrane translocation lead to conformational changes in Akt, which gets phosphorylated on Thr^{308} in the activation loop, and Ser^{473} in the hydrophobic phosphorylation motif by PDK1. This dual phosphorylation causes full activation of the enzyme. Inhibitors of PI 3-kinase and over-expression of dominant negative PI 3-kinase mutants are shown to block many of the physiological responses of a cell to insulin, indicating that PI 3-kinase lies upstream of these events. PI 3-kinase is becoming an attractive target for drug development, particularly in the areas of cancer and other proliferative diseases as well as in the treatment of inflammatory and immunological conditions.

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Phosphatidylinositol 3-Kinase (PI 3-Kinase) Inhibitors

Product	Cat. No.	Comments	Size
ET-18-OCH_3	**341207**	A non-selective weak inhibitor of PI 3-kinase (IC_{50} = 35 μM).	5 mg
LY 294002	**440202**	A cell-permeable, potent and specific inhibitor of PI 3-kinase that acts on the ATP-binding site of the enzyme (IC_{50} = 1.4 μM). Also inhibits non-homologous DNA end-joining in the 460 kDa PI-3-like kinase DNA-PKcs, which is the catalytic subunit of DNA-activated protein kinase.	5 mg
LY 294002 in Solution	**440204**	A 10 mM solution of LY 294002 (Cat. No. 440202) in anhydrous DMSO.	1 mg
LY 303511	**440203**	A negative control for the PI 3-kinase inhibitor, LY 294002 (Cat. No. 440202). Contains a single atom substitution in the morpholine ring compared to LY 294002. Does not affect PI 3-kinase activity even at concentrations ≥100 μM.	1 mg
Quercetin, Dihydrate	**551600**	An inhibitor of PI 3-kinase (IC_{50} = 3.8 μM) and phospholipase A_2 (IC_{50} = 2 μM). Also inhibits mitochondrial ATPase, phosphodiesterases, and PKC.	100 mg
Wortmannin	**681675**	A fungal metabolite that acts as a potent, selective, cell-permeable and irreversible inhibitor of PI 3-kinase in purified preparations and cytosolic fractions (IC_{50} = 5 nM). Blocks the catalytic activity of PI 3-kinase without affecting the upstream signaling events.	1 mg

Protein Kinase A (PKA; cAMP-Dependent Protein Kinase) Inhibitors

The cAMP-dependent protein kinase (protein kinase A; PKA) pathway is one of the most versatile signaling pathways in eukaryotic cells. Various extracellular signals converge on this signaling pathway through ligand binding to G protein-coupled receptors. Hence, the PKA pathway is tightly regulated at several levels to maintain specificity in the multitude of signal inputs. PKA is composed of two regulatory and two catalytic subunits. In the holoenzyme, the regulatory subunits are bound to the active site of the catalytic subunits, inactivating them. Binding of cAMP to the regulatory subunits causes a conformational change that releases and activates the two catalytic subunits. The active catalytic subunits can then phosphorylate serine and/or threonine residues on the substrates in the cytosol and in the nucleus. When the levels of cAMP begin to fall, the regulatory subunits regain their affinity towards the catalytic subunits and form the inactive holoenzyme. If cAMP levels remain persistently elevated, many cells change their behavior and may either differentiate, proliferate, or undergo apoptosis.

PKA holoenzyme exists in two forms, type I and type II. They contain identical catalytic subunits; however, their regulatory subunits differ (RI or RII dimer). Type I holoenzyme is predominantly cytosolic whereas type II holoenzyme is compartmentalized to subcellular organelles via specific anchoring proteins. The turnover rate of free type I regulatory subunit is significantly higher than that of type II subunits. When free catalytic subunit is microinjected into the cytoplasm of intact cells, it migrates to the nucleus, whereas the free regulatory subunit remains only in the cytoplasm following microinjection. When both subunits are co-injected, the regulatory subunit blocks the nuclear migration of the catalytic subunit. CREB is a major nuclear target for the catalytic subunit that binds to cAMP response elements (CREs) in the promoter regions of cAMP-responsive genes. Phosphorylation of CREB proteins alters their ability to form dimers and to interact with CREs.

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Protein Kinase A (PKA; cAMP–Dependent Protein Kinase) Inhibitors

Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	A shorter alkyl chain derivative of W-7 (Cat. No. 681629) that inhibits PKA (K_i = 4.3 μM),) casein kinase I (K_i = 80 μM), casein kinase II (K_i = 5.1 μM), MLCK (K_i = 7.4 μM), PKC (K_i = 47 μM) and PKG (K_i = 3.8 μM).	10 mg
Adenosine 3′,5′-cyclic Monophosphorothioate, Rp-Isomer, Triethylammonium Salt	**116814**	A cell-permeable inhibitor of PKA (K_i = 11 μM). Resistant to hydrolysis by phosphodiesterases.	5 μmol
Adenosine 3′,5′-cyclic Monophosphorothioate, 8-Bromo-, Rp-Isomer, Sodium Salt	**116816**	Cell-permeable antagonist of cAMP that is resistant to the action of mammalian cyclic nucleotide phosphodiesterases. Rp-8-Br-cAMPS is more lipophilic than 8-Br-cAMP and Rp-cAMPS. In contrast to other common ATP-site inhibitors or to its parent compound Rp-cAMPS, Rp-8-Br-cAMPS discriminates between both isozymes of PKA, preferring type I, thus providing additional selectivity.	5 μmol
Adenosine 3′,5′-cyclic Monophosphorothioate, 8-Bromo-2′-Monobutyryl-, Rp-Isomer, Sodium Salt	**116813**	An inhibitor of PKA that also inhibits the basal Ca^{2+} currents in smooth muscle. Reported to block the excitatory effect of 8-Bromo-cGMP (Cat No. 116816). More lipophilic and cell-permeable than Rp-8-Br-cAMPS.	5 μmol
Adenosine 3′,5′-cyclic Monophosphorothioate, 8-Chloro-, Rp-Isomer, Sodium Salt	**116819**	A cell-permeable, metabolically stable cAMP analog that acts as a competitive inhibitor of PKA. Preferentially inhibits type I PKA (IC_{50} ~50 μM).	5 μmol
Adenosine 3′,5′-cyclic Monophosphorothioate, 2′-O-Monobutyryl-, Rp-Isomer, Sodium Salt	**116825**	A cell-permeable precursor of Rp-cAMPS (Cat. No. 116814), a PKA inhibitor. Rp-MB-cAMPS is cleaved by intracellular esterases to release butyrate and Rp-cAMPS. The Rp-cAMPS binds to the cAMP binding site on PKA type I and type II, thereby prevents holoenzyme dissociation and PKA activation.	5 μmol
4-Cyano-3-methylisoquinoline	**238900**	A potent, cell-permeable, specific inhibitor of PKA (IC_{50} = 30 nM). Inhibition is competitive with respect to ATP.	1 mg
Ellagic Acid, Dihydrate	**324683**	A potent antioxidant that acts as a potent inhibitor of PKA catalytic subunit (cAK) and PKC (IC_{50} = 2 and 8 μM respectively). Also inhibits DNA topoisomerases I and II (IC_{50} = 1.8 μM and 2.1 μM, respectively).	500 mg

Protein Kinase A (PKA; cAMP-Dependent Protein Kinase) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
H-7, Dihydrochloride	**371955**	A broad based serine-threonine kinase inhibitor. Potent inhibitor of MLCK (K_i = 97 μM), PKA (K_i = 3.0 μM), PKC C (K_i = 6 μM), and PKG (K_i = 5.8 μM).	1 mg 5 mg
H-8, Dihydrochloride	**371958**	Highly active inhibitor of cyclic-nucleotide-dependent protein kinases. Inhibits MLCK (K_i = 68 μM), PKA (K_i = 1.2 μM), PKC (K_i = 15 μM), and PKG (K_i = 480 nM).	1 mg 5 mg
H-9, Dihydrochloride	**371961**	Closely resembles H-8 in its chemical structure and inhibition potency. Inhibits PKA (K_i = 1.9 μM), PKC (K_i = 18 μM), and PKG (K_i = 870 nM). Useful as a ligand for the separation and purification of these three enyzmes.	1 mg
H-89, Dihydrochloride	**371963**	A cell-permeable selective and potent inhibitor of PKA (K_i = 48 nM). Inhibits other kinases at several fold higher concentrations: MLCK (K_i = 28.3 μM), CaM kinase II (K_i = 29.7 μM), PKC (K_i = 31.7 μM), casein kinase I (K_i = 38.3 μM), and Rho Kinase II (IC_{50} = 270 nM).	1 mg
H-89, Dihydrochloride in Solution	**371962**	A 10 mM solution of H-89, Dihydrochloride (Cat. No. 371963) in anhydrous DMSO.	1 mg
HA 1004, Dihydrochloride	**371964**	A novel intracellular Ca^{2+} antagonist that inhibits CaM Kinase II (K_i = 13 μM), MLCK (K_i = 150 μM), PKA (K_i = 2.3 μM), PKC (K_i = 40 μM), and PKG (K_i = 1.3 μM).	1 mg
HA 1077, Dihydrochloride	**371970**	Cell-permeable Ca^{2+} antagonist that inhibits PKA (IC_{50} = 1.6 μM), PKG (IC_{50} = 1.6 μM), and MLCK (IC_{50} = 3.6 μM). Also reported to potently inhibit Rho-associated kinase.	1 mg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable inhibitor of CaM kinase II (K_i = 1.8 nM), MLCK (K_i = 17 nM), PKA (K_i = 18 nM), PKC (K_i = 25 nM), and PKG (K_i = 20 nM). Also acts as a potent inhibitor (IC_{50} = 3 nM) of the tyrosine protein kinase activity of the NGF receptor gp 140trk, the product of the trk protooncogene.	100 μg
K-252b, *Nocardiopsis* sp.	**420319**	A non-selective inhibitor of MLCK (K_i = 147 nM), PKA (K_i = 90 nM), PKC (K_i = 20 nM), and PKG (K_i = 100 nM).	50 μg 100 μg
KT5720	**420320**	Prepared by a chemical modification of K-252a. Potent specific cell-permeable inhibitor of PKA (K_i = 56 nM) that does not significantly affect the activity of PKC, PKG, or MLCK.	50 μg 100 μg
KT5720 in Solution	**420323**	A 2 mM solution of KT5720 (Cat. No. 420320) in anhydrous DMSO.	50 μg
Piceatannol	**527948**	A plant metabolite that preferentially inhibits the activity of p72Syk (IC_{50} ~10 μM). Also inhibits rat liver PKA catalytic subunit (cAK) (IC_{50} = 3 μM), PKC (IC_{50} = 8 μM), MLCK (IC_{50} = 12 μM) and wheat embryo Ca^{2+}/dependent protein kinase (IC_{50} = 19 μM).	1 mg
Protein Kinase A Heat Stable Inhibitor, Isoform α, Rabbit, Recombinant, *E. coli*	**539488**	A 77 amino acid protein that is a highly specific inhibitor of the PKA catalytic subunit (K_i = 98 pM). It is not known to inhibit any other serine/threonine kinases.	250 U
Protein Kinase A Inhibitor (5-24)	**116805**	Peptide corresponding to the active site on the skeletal muscle inhibitor protein. Competitive inhibitor of PKA (K_i = 2.3 nM).	500 μg
Protein Kinase A Inhibitor 6-22 Amide	**539684**	A potent and competitive inhibitor of PKA (K_i = 1.7 nM).	1 mg
Protein Kinase A Inhibitor 14-22 Amide, Cell-Permeable, Myristoylated	**476485**	A heat-stable protein kinase inhibitor (PKI) peptide sequence (14-22) that has been myristoylated at the N-terminus, enhancing its cell-permeability. The non-myristoylated version of this peptide is shown to be a highly specific inhibitor of PKA (K_i = 36 nM).	500 μg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable broad spectrum inhibitor of protein kinases. Inhibits CaM kinase (IC_{50} = 20 nM), MLCK (IC_{50} = 1.3 nM), PKA (IC_{50} = 7 nM), PKC (IC_{50} = 0.7 nM), and PKG (IC_{50} = 8.5 nM).	100 μg 250 μg
Staurosporine, *Streptomyces* sp. in Solution	**569396**	A 1 mM solution of Staurosporine, *Streptomyces* sp. (Cat. No. 569397) in anhydrous DMSO.	100 μg
TX-1123	**655200**	A cell-permeable inhibitor of PKA (IC_{50} = 9.6 μM). Also acts as an inhibitor of Src, and eEF2-K (IC_{50} = 2.2 and 3.2 μM, respectively).	10 mg

Protein Kinase C (PKC) Inhibitors

Protein kinase C (PKC), a ubiquitous, phospholipid-dependent enzyme, is involved in signal transduction associated with cell proliferation, differentiation, and apoptosis. At least eleven closely related PKC isozymes have been reported that differ in their structure, biochemical properties, tissue distribution, subcellular localization, and substrate specificity. They are classified as conventional (α, β_1, β_2, γ), novel (δ, ε, η, θ, μ), and atypical (ζ, λ) isozymes. Conventional PKC isozymes are Ca^{2+}-dependent, while novel and atypical isozymes do not require Ca^{2+} for their activation. All PKC isozymes, with the exception of ζ and λ, are activated by diacylglycerol (DAG). PKC isozymes negatively or positively regulate critical cell cycle transitions, including cell cycle entry and exit and the G_1 and G_2 checkpoints.

In its unstimulated state, most of the PKC resides in the cytosol. In this state, the pseudosubstrate sequence of the regulatory domain of PKC interacts with the catalytic domain and prevents access of the substrate to the catalytic site. Binding of a hormone or other effector molecule to the membrane receptor results in activation of phospholipase C (PLC) or phospholipase A_2 (PLA_2) via a G-protein-dependent phenomenon. The activated PLC hydrolyzes phosphatidylinositol-4, 5-bisphosphate (PIP_2) to produce DAG and inositol-1,4,5-trisphosphate (IP_3). The IP_3 causes the release of endogenous Ca^{2+} that binds to the cytosolic PKC and exposes the phospholipid-binding site. The binding of Ca^{2+} translocates PKC to the membrane, where it interacts with DAG and is transformed into a fully active enzyme.

Altered PKC activity has been linked with various types of malignancies. Higher levels of PKC and differential activation of various PKC isozymes have been reported in breast tumors, adenomatous pituitaries, thyroid cancer tissue, leukemic cells, and lung cancer cells. Down-regulation of PKCα is reported in the majority of colon adenocarcinomas and in the early stages of intestinal carcinogenesis. Thus, PKC inhibitors have become important tools in the treatment of cancers. The involvement of PKC in the regulation of apoptosis adds another dimension to the effort to develop drugs that will specifically target PKC.

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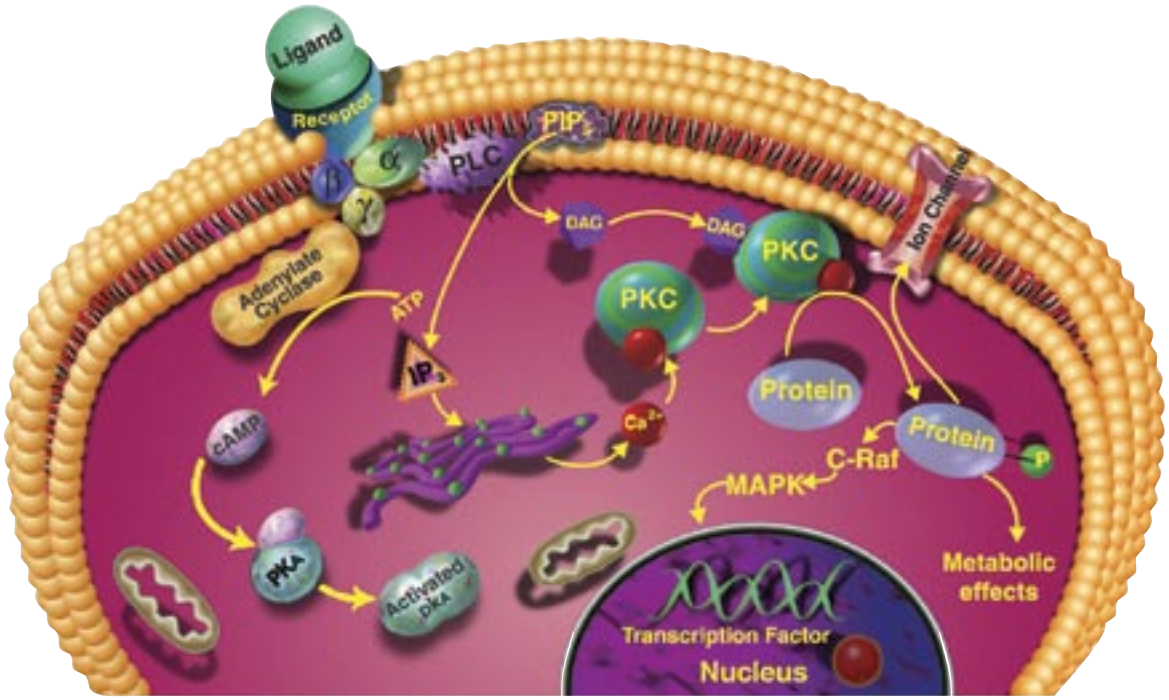

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Table 1: Isozyme Specificities of Selected Protein Kinase C Inhibitors (IC_{50} values are in μM)

Product	Cat. No.	PKC_α	PKC_β	$PKC_{\beta I}$	$PKC_{\beta II}$	PKC_γ	PKC_δ	PKC_ε	PKC_ξ	PKC_μ	PKC_η
Bisindolylmaleimide I (Gö 6850)	**203290**	0.008	–	0.018	–	–	0.21	0.132	5.8	–	–
CGP41251	**–**	0.024	–	0.017	0.032	0.018	0.360	4.50	>1000	–	0.060
Gö 6976	**365250**	0.0023	–	0.006	–	–	–	–	–	0.02	–
Gö 6983	**365251**	0.007	0.007	–	–	0.006	0.01	–	0.06	20	–
LY333531	**–**	0.360	–	0.0047	0.0059	0.400	0.250	0.600	$>10^5$	–	0.052
Ro-31-7549	**557508**	0.053		0.195	0.163	0.213	–	0.175	–	–	–
Ro-31-8220	**557520**	0.005	–	0.024	0.014	0.027	–	0.024	–	–	–
Ro-31-8425	**557514**	0.008	–	0.008	0.014	0.013	–	0.039	–	–	–
Ro-32-0432	**557525**	0.009	–	0.028	0.031	0.037	–	0.108	–	–	–
Rottlerin	**557370**	30	42	–	–	40	3 - 6	100	100	–	–
Staurosporine	**569397**	0.028	–	0.013	0.011	0.032	0.028	0.025	>1.5	–	–
UCN01	**–**	0.029	–	0.034	–	0.030	0.590	0.530	–	–	–

Protein Kinase C (PKC) Inhibitors

Product	Cat. No.	Comments	Size
Bisindolylmaleimide I (GF 109203X; Gö 6850)	**203290**	A highly selective cell-permeable PKC inhibitor (K_i = 10 nM) that is structurally similar to staurosporine. Acts as a competitive inhibitor for the ATP-binding site of PKC. Shows high selectivity for PKCα, β_I, β_{II}, γ, δ, and ε isozymes. May inhibit protein kinase A at a much higher concentration (K_i = 2 μM).	250 μg 1 mg
Bisindolylmaleimide I in Solution	**203293**	A 1 mg/ml solution of Bisindolylmaleimide I (Cat. No. 203290) in anhydrous DMSO.	1 ml
Bisindolylmaleimide I, Hydrochloride	**203291**	An inhibitor of PKC (K_i = 10 nM). Inhibits PKA at much higher concentrations (K_i = 2 μM). An enhanced water-soluble form of Bisindolylmaleimide I (Cat. No. 203290).	250 μg 1 mg
Bisindolylmaleimide II	**203292**	A potent and selective inhibitor of PKC (IC_{50} = 13 nM). Also inhibits PKA at much higher concentrations (IC_{50} = 2 μM).	1 mg
Bisindolylmaleimide III, Hydrochloride	**203294**	A potent and selective inhibitor of PKC (IC_{50} = 26 nM). It also inhibits PKA at much higher concentrations (IC_{50} = 500 nM).	250 μg 1 mg
Bisindolylmaleimide IV	**203297**	A potent and selective inhibitor of PKC (IC_{50} = 87 nM) and PKA (IC_{50} = 2.7 μM).	250 μg 1 mg
Bisindolylmaleimide V	**203303**	Useful as a negative control compound for PKC inhibition studies (IC_{50} >100 μM). Blocks the activation of $p70^{s6k}$/$p85^{s6k}$ *in vivo* (IC_{50} = 8 μM).	250 μg 1 mg
Calphostin C, *Cladosporium cladosporioides*	**208725**	Cell-permeable, highly specific inhibitor of PKC (IC_{50} = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. At higher concentrations inhibits MLCK (IC_{50} > 5 μM), PKA (IC_{50} > 50 μM), PKG (IC_{50} >25 μM), and $p60^{v\text{-}src}$ protein tyrosine kinase (IC_{50} > 50 μM). Does not compete with Ca^{2+} or phospholipids.	50 μg 100 μg
Cardiotoxin, *Naja nigricollis*	**217504**	A cytolytic toxin that causes depolarization of skeletal muscle fibers *in vitro*. Stimulates Ca^{2+} transport and ATP hydrolysis by sarcolemmal Ca^{2+}/Mg^{2+}-ATPase. Its action is strongly potentiated by phospholipase A_2. Inhibits PKC (IC_{50} = 1.8 μM).	1 mg
Chelerythrine Chloride	**220285**	Naturally occurring alkaloid. Cell-permeable, selective inhibitor of PKC (IC_{50} = 660 nM). Acts on the catalytic domain irrespective of the attachment of the regulatory domain. Material is a competitive inhibitor with respect to the phosphate acceptor and a non-competitive inhibitor with respect to ATP. Over ten-fold more potent than H-7, HCl (Cat. No. 371955).	5 mg
Dequalinium Chloride (DECA)	**263225**	An anti-tumor agent and PKC inhibitor. When exposed to UV light, DECA covalently and irreversibly inhibits PKC_α or PKC_β (IC_{50} = 7-18 μM).	500 mg

Protein Kinase C (PKC) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Ellagic Acid, Dihydrate	**324683**	A potent antioxidant with anti-mutagenic and anti-carcinogenic properties. Inhibits DNA topoisomerases I and II (IC_{50} = 1.8 μM and 2.1 μM, respectively). Acts as a potent inhibitor of PKA catalytic subunit (cAK) and PKC (IC_{50} = 2 and 8 μM respectively).	500 mg
Gossypol, Cotton Seeds	**368400**	A cell-permeable, polyphenolic aldehyde isolated from cotton seeds that is shown to inhibit growth of cultured mammalian cells. Shown to block dynein ATPase, PKC and PKA activities.	25 mg
Gö 6976	**365250**	An inhibitor of PKC (IC_{50} = 7.9 nM for rat brain). Selectively inhibits Ca^{2+}-dependent PKC α-isozyme (IC_{50} = 2.3 nM) and $PKC_{βI}$ (IC_{50} = 6.2 nM). Does not affect the kinase activity of the Ca^{2+}-independent PKC δ-, ε-, and ζ-isoenzymes even at micromolar levels.	500 μg
Gö 6976 in Solution	**365253**	A 500 μg/ml solution of Gö 6976 (Cat. No. 365250) in anhydrous DMSO.	1 ml
Gö 6983	**365251**	A potent inhibitor of PKC that has been shown to selectively inhibit several PKC isozymes (IC_{50} = 7 nM for $PKC_α$ and $PKC_β$; 6 nM for $PKC_γ$; 10 nM for $PKC_δ$; 60 nM for $PKC_ζ$). Gö 6983 does not effectively inhibit $PKC_μ$ (IC_{50} = 20 μM) and can thus be used to differentiate $PKC_μ$ from other PKC isozymes.	500 μg
Gö 7874, Hydrochloride	**365252**	A potent and selective inhibitor of rat brain PKC (IC_{50} = 4 nM) versus MLCK (IC_{50} = 120 nM), PKA (IC_{50} = 150 nM), and PKG (IC_{50} = 4.8 μM).	500 μg
H-7, Dihydrochloride	**371955**	A broad based serine-threonine kinase inhibitor. Potent inhibitor of MLCK (K_i = 97 μM), PKA (K_i = 3 μM), PKC (K_i = 6 μM), and PKG (K_i = 5.8 μM).	1 mg 5 mg
Iso-H-7, Dihydrochloride	**371956**	Less potent than H-7 in inhibiting rat brain PKC isoforms (IC_{50} = 50 μM). Also inhibits other cyclic-nucleotide-dependent protein kinases.	1 mg
HBDDE	**372770**	An inhibitor of PKC that selectively inhibits $PKC_α$ (IC_{50} = 43 μM) and $PKC_γ$ (IC_{50} = 50 μM) over $PKC_δ$, $β_I$ and $β_{II}$ isozymes.	1 mg
1-O-Hexadecyl-2-O-methyl-*rac*-glycerol	**430240**	A novel inhibitor of PKC (IC_{50} = 80 μM).	250 mg
Hispidin	**377980**	A potent inhibitor of $PKC_β$ isoform ($PKC_β$; IC_{50} = 2 μM).	2 mg
Hypericin	**400076**	A polycyclic dione that inhibits PKC (IC_{50} = 3.3 μM). Also known to inhibit the protein tyrosine kinase activities of the insulin receptor (IC_{50} = 20 - 29 nM), the EGFR (IC_{50} = 35 nM), casein kinase II (IC_{50} = 6 nM), and MAP kinase (IC_{50} = 4 nM). Useful probe for PKC due to its bright red fluorescence emission and photostability.	1 mg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable protein kinase inhibitor that inhibits CaM kinase II (K_i = 1.8 nM), MLCK (K_i = 17 nM), PKA (K_i = 18 nM), PKC (K_i = 25 nM), and PKG (K_i = 20 nM).	100 μg
K-252b, *Nocardiopsis* sp.	**420319**	A non-selective inhibitor of MLCK (K_i = 147 nM), PKA (K_i = 90 nM), PKC (K_i = 20 nM), and PKG (K_i = 100 nM).	50 μg 100 μg
K-252c	**420305**	Inhibits PKA (IC_{50} = 25.7 μM) and PKC (IC_{50} = 2.45 μM).	1 mg
Myristoylated EGF-R Fragment (651-658), PKC Inhibitor	**476475**	Epidermal growth-factor receptor (EGF-R) conserved sequence that is identical to v-*erb*B (95-102). An N-terminal myristoylated membrane-permeable inhibitor that inhibits PKC (IC_{50} = 5 μM) in intact cells.	500 μg
NGIC-I	**481500**	A potent and selective inhibitor of PKC (IC_{50} = 75 nM) versus PKA (IC_{50} >10 μM) and PKG (IC_{50} = 320 nM).	500 μg
Phloretin	**524488**	A flavonoid that prevents the activation of PKC.	200 mg
Piceatannol	**527948**	A plant metabolite that preferentially inhibits the activity of p72Syk (IC_{50} ~10 μM). Also acts as an inhibitor of the rat liver PKA catalytic subunit (cAK) (IC_{50} = 3 μM), PKC (IC_{50} = 8 μM), MLCK (IC_{50} = 12 μM) and wheat embryo Ca^{2+}-dependent protein kinase (CDPK) (IC_{50} = 19 μM).	1 mg
Polymyxin B Sulfate	**5291**	An antibiotic that inhibits phospholipid sensitive Ca^{2+}-dependent protein kinase. Mixture of polymyxin B_1 sulfate and polymyxin B_2 sulfate.	500 mg 1 g 5 g
Protein Kinase C Inhibitor (20 - 28), Cell-Permeable, Myristoylated	**476480**	Pseudosubstrate sequence from $PKC_α$ and $PKC_β$. N-terminal myristoylated to allow membrane permeability. Highly specific inhibitor of TPA activation of MARCKS phosphorylation in fibroblast primary cultures (IC_{50} = 8 μM). Exhibits 98% inhibition at 100 μM.	500 μg

Protein Kinase C Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Protein Kinase C Inhibitor Peptide 19-31	**05-23-4904**	More potent inhibitor of PKC (IC_{50} = 100 nM) than PKC Inhibitor 19-36 (Cat. No. 539560).	1 mg 5 mg
Protein Kinase C Inhibitor Peptide 19-36	**539560**	Acts as a pseudo-substrate by binding to the active sites of protein kinases. Potent inhibitor of PKC (K_i = 147 nM) but not of PKA (IC_{50} = 423 µM).	500 µg 1 mg
Protein Kinase C_β C2-4 Inhibitor	**539561**	A nonapeptide derived from the RACK1 binding site in the C2 domain of PKC_β (218-226). Inhibits glucose-induced translocation of PKC_β to the cell periphery and reduces insulin response to glucose. Also inhibits phorbol ester-induced translocation of C2-containing isoenzymes in permeabilized cells.	1 mg
Protein Kinase C_η Pseudosubstrate Inhibitor	**539602**	A PKC_η pseudosubstrate sequence peptide that can be used as a competitive inhibitor in *in vitro* PKC_η kinase assays.	500 µg
Protein Kinase C_η Pseudosubstrate Inhibitor, Myristoylated	**539604**	A cell-permeable myristoylated PKC_η pseudo-substrate sequence peptide (Cat. No. 539602). Useful for studies of PKC_η function in intact cells.	500 µg
Protein Kinase C_ζ Pseudosubstrate Inhibitor	**539610**	A non-cell-permeable PKC_ζ pseudosubstrate sequence peptide that can be used as a competitive inhibitor PKC_ζ in *in vitro* kinase assays.	500 µg
Protein Kinase C_ζ Pseudosubstrate Inhibitor, Myristoylated	**539624**	A cell-permeable myristoylated form of PKC_ζ pseudo-substrate peptide (Cat. No. 539610) that includes amino acids 113 to 125 of the pseudosubstrate region. Useful for inhibition studies of PKC_ζ in intact cells.	500 µg
Protein Kinase C_θ Pseudosubstrate Inhibitor, Myristoylated	**539636**	A cell-permeable myristoylated PKC_θ pseudosubstrate sequence peptide (Cat. No. 539634). Useful for studies of PKC_θ function in intact cells.	500 µg
Protein Kinase C_ε Translocation Inhibitor Peptide	**539522**	An octapeptide that selectively inhibits the translocation of PKC_ε to subcellular sites. Inhibition of PKC_ε translocation is known to specifically block phorbol ester or norepinephrine-mediated regulation of contraction in cardiomyocytes.	5 mg
Protein Kinase C_ε Translocation Inhibitor Peptide, Negative Control	**539542**	A scramble peptide with an identical amino acid composition to that of PKC_ε Translocation Inhibitor Peptide (Cat. No. 539522). Useful as a negative control for this PKC_ε translocation inhibitor.	5 mg
Ro-31-7549	**557508**	A selective PKC inhibitor that acts at the ATP binding site of PKC (IC_{50} = 158 nM for rat brain PKC). IC_{50} values for individual PKC isozymes are as follows: 53 nM for PKC_α, 195 nM for $PKC_{\beta I}$, 163 nM for $PKC_{\beta II}$, 213 nM for PKC_γ, and 175 nM for PKC_ε.	1 mg
Ro-31-7549, Immobilized	**557509**	An immobilized form of the PKC inhibitor Ro-31-7549 (Cat. No. 557508) that is covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. Useful to affinity-precipitate PKC and other functionally related proteins from cell or tissue extracts. Binding capacity: ≥3 mg purified PKC_α per gram of dry beads.	1 set
Ro-31-8220	**557520**	A competitive, selective inhibitor of PKC (IC_{50} = 10 nM) over PKA (IC_{50} = 900 nM), CaM kinase (IC_{50} = 17 µM) and phosphorylase protein kinase.	500 µg
Ro-31-8425	**557514**	A potent and selective inhibitor of PKC (IC_{50} = 15 nM for rat brain PKC). Exhibits some degree of isozyme specificity (IC_{50} = 8 nM for PKC_α, 8 nM for $PKC_{\beta I}$, 14 nM for $PKC_{\beta II}$, 13 nM for PKC_γ, and 39 nM for PKC_ε). Shows slight selectivity for the conventional PKC isozymes PKC_α, PKC_β, and PKC_γ over the Ca^{2+}-independent PKC isozyme PKC_ε.	1 mg
Ro-32-0432	**557525**	A selective cell-permeable PKC inhibitor. Displays about a 10-fold greater selectivity for PKC_α (IC_{50} = 9 nM) and a 4-fold greater selectivity for $PKC_{\beta I}$ (IC_{50} = 28 nM) over PKC_ε (IC_{50} = 108 nM).	500 µg 1 mg
Rottlerin	**557370**	An inhibitor of PKC_δ (IC_{50} = 3-6 µM) and PKC_θ. Also inhibits PKC_α, PKC_β, and PKC_γ isoforms, but with significantly reduced potency (IC_{50} = 30-42 µM). Has reduced inhibitory activity on PKC_ε, PKC_η, and PKC_ξ (IC_{50} = 80-100 µM). Also known to inhibit CaM kinase III (IC_{50} = 5.3 µM).	10 mg
Safingol	**559300**	A *lyso*-sphingolipid PKC inhibitor that competitively interacts at the regulatory phorbol binding domain of PKC. Inhibits enzymatic activity and ^{3}H-phorbol dibutyrate binding of purified rat brain PKC (IC_{50} = 37.5 µM and 31 µM, respectively). Inhibits human PKC_α in MCF-7 DOXR cells (IC_{50} = 40 µM).	1 mg
Sangivamycin	**559307**	A cytotoxic purine nucleoside that acts as a selective and potent inhibitor of PKC (IC_{50} = 10 µM). The inhibition is competitive with respect to ATP and non-competitive with respect to histone and lipid cofactors.	1 mg

Protein Kinase C Inhibitors, *continued*

Product	Cat. No.	Comments	Size
D-*erythro*-Sphingosine, Free Base, Bovine Brain	**567725**	A potent and selective inhibitor of PKC (PKC; IC_{50} = 2.8 μM) and insulin receptor tyrosine kinase. PKC inhibition is competitive with respect to diacyglycerol, phorbol dibutyrate, and Ca^{2+}.	10 mg
D-*erythro*-Sphingosine, Free Base, Bovine Brain, High Purity	**567726**	A highly purified preparation of Cat. No. 567725 containing >99% of the *erythro* isomer. A potent and selective inhibitor of PKC (IC_{50} = 2.8 μM) and insulin receptor tyrosine kinase. PKC inhibition is competitive with respect to diacylglycerol, phorbol dibutyrate, and Ca^{2+}.	10 mg
D-*erythro*-Sphingosine, Dihydro-	**300230**	Biosynthetic precursor of sphingosine. Inhibits PKC in Chinese hamster ovary cells (IC_{50} = 2.9 μM).	10 mg
D-*erythro*-Sphingosine, N,N-Dimethyl-	**310500**	A PKC inhibitor (IC_{50} = 12 μM) that also enhances *src* kinase activity.	5 mg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable broad spectrum inhibitor of protein kinases. Inhibits CaM kinase (IC_{50} = 20 nM), MLCK (IC_{50} = 1.3 nM), PKA (IC_{50} = 7 nM), PKC (IC_{50} = 700 pM), and PKG (IC_{50} = 8.5 nM).	100 μg 250 μg
Tamoxifen Citrate	**579000**	A potent synthetic anti-estrogen. A reversible inhibitor of PKC (IC_{50} = 10 μM).	100 mg
Tamoxifen, 4-Hydroxy-, (Z)-	**579002**	An active metabolite of the widely used therapeutic anti-estrogen agent, tamoxifen (Cat. No. 579000) that is more potent than the parent compound. Inhibits PKC by modifying its catalytic domain.	5 mg
TER14687	**581800**	Blocks the interaction between PKC_{θ}-VI and p59fyn in the yeast two-hybrid system and in T-cells. Prevents OKT3-induced translocation of PKC_{θ} in T cells. Does not affect any other PKC isozymes in Jurkat or normal T cells.	10 mg
Vitamin E Succinate	**679130**	Shown to modulate adenylate cyclase activity and inhibit PKC activity.	100 mg

Serine/Threonine Kinase Inhibitor Set

A set of 6 vials. Each set contains 250 μg of PKC inhibitor, Bisindolylmaleimide I (Cat. No. 203290); 1 mg of PKA inhibitor, H-89, Dihydrochloride (Cat. No. 371963); 1 mg of PKG inhibitor, Protein Kinase G Inhibitor (Cat. No. 370654); 1 mg of MLCK inhibitor, ML-7 (Cat. No. 475880); 1 mg of CaM kinase II inhibitor, KN-93 (Cat. No. 422708); and 100 μg of the broad range inhibitor, Staurosporine (Cat. No. 569397). Not available for sale in Japan.

Cat. No. 539572 1 set

Protein Kinase C Inhibitor Set

A set of 6 vials. Each set contains 250 μg of Bisindolylmaleimide I (Cat. No. 203290), 50 μg of Calphostin C, *Cladosporium cladosporioides* (Cat. No. 208725), 5 mg of Chelerythrine Chloride (Cat. No. 220285), 500 μg of Gö 6976 (Cat. No. 365250), 500 μg of Myristoylated Protein Kinase C Inhibitor 20-28, Cell-Permeable (Cat. No. 476480), and 500 μg of Ro-32-0432 (Cat. No. 557525).

Cat. No. 539573 1 set

Also Available...

NEW! Recombinant PKC Isozymes

NEW! **Protein Kinase C_{α}, His•Tag™, Human, Recombinant**
Cat. No. 539651 5 μg
20 μg

NEW! **Protein Kinase $C_{\beta II}$, His•Tag™, Human, Recombinant**
Cat. No. 539658 5 μg
20 μg

NEW! **Protein Kinase C_{δ}, His•Tag™, Human, Recombinant**
Cat. No. 539678 5 μg
20 μg

Protein Kinase G (PKG; cGMP-Dependent Protein Kinase) Inhibitors

cGMP produces its effects by interacting with intracellular receptor proteins. A primary action of elevated cGMP levels is the stimulation of cGMP-dependent protein kinase (PKG) that catalyzes the phosphorylation of a number of physiologically relevant proteins involved in contractile activity of smooth muscle cells. The mammalian PKG family consists of PKGIα and Iβ, splice forms derived from one gene, and PKGII, encoded by a second gene. They are ubiquitous effector enzymes that regulate a variety of physiological processes in response to nitric oxide and natriuretic agonists.

Cells of the cardiovascular system such as fibroblasts and certain types of endothelial cells contain PKGI. Smooth muscle cells are rich in PKGIα and Iβ, platelets and T lymphocytes contain PKGIβ, and cardiac myocytes contain PKGIα. It is important to note that PKGs are lost in many primary cell types upon passaging in cell culture and may not be detected in many cell lines. Studies have shown that cultured vascular smooth muscle cells (VSMCs) may stop expressing PKG and acquire a non-contractile phenotype. The restoration of PKG expression can result in the cells acquiring a more contractile phenotype. This is an important observation because several vascular disorders result from accumulation of non-contractile VSMC in the vessel wall. In endothelial cells PKGI phosphorylates and activates eNOS, which reduces its Ca^{2+}-dependence. Also, in endothelial cells, PKGI and PKGII are known to phosphorylate, 6-pyruvoyltetrahydropterin synthase that produces tetrahydrobiopterin, a required co-factor for eNOS activation.

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Protein Kinase G (PKG; cGMP–Depenent Protein Kinase) Inhibitors

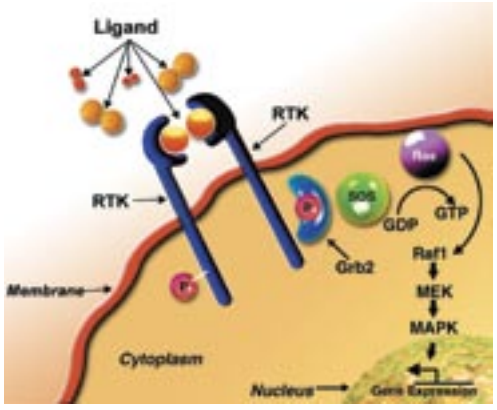
Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	A shorter alkyl chain derivative of W-7 (Cat. No. 681629) that inhibits PKG (K_i = 3.8 μM), casein kinase I (K_i = 80 μM), casein kinase II (K_i = 5.1 μM), MLCK (K_i = 7.4 μM), PKA (K_i = 4.3 μM), and PKC (K_i = 47 μM).	10 mg
Drosophila Antennapedia Homeo-Domain (43-58)	**287895**	The membrane translocation signal sequence from *Drosophila* Antennapedia homeo-domain (43-58) that inhibits PKGIα (K_i = 970 nM). Does not exhibit significant inhibition against PKA (K_i = 107 μM).	1 mg
Guanosine 3′,5′-cyclic Monophosphorothioate, Rp-Isomer, Triethylammonium Salt	**370666**	A competitive inhibitor of PKGIα that blocks PKG and PKA activation (K_i = 20 μM). Exhibits low cell permeability.	5 μmol
Guanosine 3′,5′-cyclic Monophosphorothioate, 8-Bromo-, Rp-Isomer, Sodium Salt	**370674**	A potent cell-permeable, metabolically stable inhibitor of PKG. Significantly more lipophilic and membrane-permeable than cGMP or Rp-cGMPS. Resistant to mammalian cyclic nucleotide-dependent phosphodiesterases.	5 μmol
Guanosine, 3′,5′-cyclic Monophosphorothioate, 8-(4-Chlorophenylthio)-, Rp-Isomer, Triethylammonium Salt	**370677**	A potent, cell-permeable inhibitor of PKG Iα, Iβ, and type II. A combination of the protein kinase inhibitor Rp-cGMPS and the widely used cGMP analog, 8-*p*CPT-cGMP. Significantly more lipophilic and membrane-permeant than Rp-cGMPS and Rp-8-Br-cGMPS. Resistant to hydrolysis by mammalian cyclic nucleotide dependent phosphodiesterases.	1 μmol
Guanosine 3′,5′-cyclic Monophosphorothioate, β-Phenyl-1, N2-etheno-8-bromo-, Rp-Isomer, Sodium Salt	**370679**	A metabolically-stable, competitive inhibitor of PKGIα and Iβ (K_i = 30 nM). Also reported to block the activation of purified PKA type II (K_i = 10 μM). More lipophilic and cell-permeable than Rp-8-*p*CPT-cGMPS (Cat. No. 370677).	1 μmol
H-7, Dihydrochloride	**371955**	A potent inhibitor of PKG (K_i = 5.8 μM), MLCK (K_i = 97 μM), PKA (K_i = 3.0 μM), and PKC (K_i = 6 μM).	1 mg 5 mg
H-9, Dihydrochloride	**371961**	An inhibitor of PKG (K_i = 870 nM), PKA (K_i = 1.9 μM), and PKC (K_i = 18.0 μM). Useful as a ligand for the separation and purification of these three enzymes.	1 mg
H-9, Immobilized	**371966**	An immobilized form of the protein kinase inhibitor H-9 (Cat. No. 371961) covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. 1 set = 25 mg of H-9 Immobilized beads and 25 mg of control beads.	1 set

Protein Kinase G (PKG; cGMP-Depenent Protein Kinase) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
HA 1004, Dihydrochloride	**371964**	An inhibitor of PKG (K_i = 1.3 μM), CaM kinase II (K_i = 13 μM), MLCK (K_i = 150 μM), PKA (K_i = 2.3 μM), and PKC (K_i = 40 μM).	1 mg
HA 1077, Dihydrochloride	**371970**	An inhibitor of PKG (IC_{50} = 1.6 μM), PKA (IC_{50} = 1.6 μM), and MLCK (IC_{50} = 3.6 μM). Also reported to potently inhibit Rho-associated kinase (ROCK).	1 mg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable inhibitor of PKG (K_i = 20 nM), CaM kinase II (K_i = 1.8 nM), MLCK (K_i = 17 nM), PKA (K_i = 18 nM), and PKC (K_i = 25 nM).	100 μg
K-252b, *Nocardiopsis* sp.	**420319**	An inhibitor of PKG (K_i = 100 nM), MLCK (K_i = 147 nM), PKA (K_i = 90 nM), and PKC (K_i = 20 nM).	50 μg 100 μg
KT5823	**420321**	A cell-permeable, highly specific inhibitor of PKG (K_i = 234 nM). Inhibits PKC (K_i = 4.0 μM) and PKA (K_i >10.0 μM) at higher concentrations.	50 μg 100 μg
Protein Kinase G Inhibitor	**370654**	A specific inhibitor of PKG (K_i = 86 μM) relative to PKA (K_i = 550 μM). Sequence corresponds to a non-phosphorylatable analog (Ser^{32} to Ala^{32}) of histone H2B (residues 29-35).	1 mg
Protein Kinase G Iα Inhibitor, Cell-Permeable	**370655**	A highly potent, membrane-permeable peptide that selectively inhibits PKG Iα (K_i = 25 nM). Inhibitor peptide is fused to the *Drosophila* Antennapedia homeo domain peptide to allow membrane permeability.	1 mg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable broad-spectrum inhibitor of protein kinases. Inhibits PKG (IC_{50} = 8.5 nM), CaM kinase (IC_{50} = 20 nM), MLCK (IC_{50} = 1.3 nM), PKA (IC_{50} = 7 nM), and PKC (IC_{50} = 700 pM).	100 μg 250 μg

Protein Tyrosine Kinase (PTK) Inhibitors

Protein tyrosine kinases (PTKs) play a key role in the regulation of cell proliferation, differentiation, metabolism, migration, and survival. They are classified as receptor PTKs and non-receptor PTKs. Receptor PTKs contain a single polypeptide chain with a transmembrane segment. The extracellular end of this segment contains a high affinity ligand-binding domain, while the cytoplasmic end comprises the catalytic core and the regulatory sequences. The cytosolic end also contains tyrosine residues, which become substrates or targets for the tyrosine kinase portion of the receptor. PTK remains inactive until a ligand binds to the receptor, which leads to the dimerization of two ligand-bound receptors (exception: insulin receptor). Once activated, receptors are able to autophosphorylate tyrosine residues outside the catalytic domain. This stabilizes the active receptor conformation and creates phosphotyrosine-docking sites for proteins that transduce signals within the cell. The cytosolic portion of the phosphorylated receptor recruits a number of cytosolic adapter proteins via interactions between phosphorylated tyrosine residues on the receptor and the SH2 domain on the adapter molecule. Different proteins have different SH2 domains that recognize specific phosphotyrosine residues. An SH2-containing protein, Grb2, acts as a common adapter protein in a majority of growth factor related signaling events.



Grb2 binding to phosphotyrosine residues changes its conformation and allows it to bind to proline-rich sequences in the carboxy terminal tail of Sos, a GDP-GTP exchange protein. This binding displaces an inhibitory domain in Sos and allows the activation of Sos, which then translocates to the plasma membrane to cause an exchange of GDP for GTP and activates Ras. A wide variety of effectors of Ras activation have been reported; however, activation of Raf, a cytoplasmic protein kinase, is one of the best-studied examples. Ras binds to the N-terminus of Raf and recruits it to the inner surface of the plasma membrane, where it is phosphorylated by protein kinase C. Translocation of Raf to the membrane positions it in direct proximity to MAP kinase kinase (MEK). Raf phosphorylates MEK, which in turn phosphorylates MAP kinase (MAPK). In a resting cell, MAPK remains inactive because its phosphorylation lip excludes ATP access to the binding pocket. However, MEK binding destabilizes the lip and exposes the buried tyrosine residues. Phosphorylation of the exposed tyrosine and the nearby threonine residues cause the lip to alter its conformation allowing ATP binding.

Non-receptor tyrosine kinases include members of the Src, Tec, JAK, Fes, Abl, FAK, Csk, and Syk families. They are located in the cytoplasm as well as in the nucleus. They exhibit distinct kinase regulation, substrate phosphorylation, and function. Deregulation of these kinases has also been linked to several human diseases. In most cases, their activation also begins with the phosphorylation of a tyrosine residue present in an activation loop. The best studied enzymes in this group include Src kinases. Src is believed to be negatively regulated by phosphorylation at Tyr^{527} present at the C-terminus by Csk and other cellular kinases. The enzyme assumes an inactive conformation when this phosphotyrosine is bound by the Src SH2 domain in an intramolecular fashion. In this structure, the Src SH3 domain interacts with a single proline, Pro^{250}, in the linker region between the SH2 and catalytic domain. In contrast to Src, c-Abl kinase activity is stimulated by phosphorylation of a catalytic domain tyrosine residue, Tyr^{412}, either via autophosphorylation or transphosphorylation by c-Src. Recent studies have indicated that dimerization or oligomerization of c-Abl might also be sufficient to activate Abl kinase activity *in vivo*.

Due to their involvement in various forms of cancers, PTKs have become prominent targets for therapeutic intervention. Selective receptor and non-receptor PTK inhibitors represent a promising class of anti-tumor agents. These agents are shown to inhibit multiple features of cancer cells, including proliferation, survival, invasion, and angiogenesis.

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Protein Tyrosine Kinase (PTK) Inhibitors

Product	Cat. No.	Comments	Size
AG 9	**658390**	Inactive inhibitor that can be used as a negative control for inhibition of EGFR (IC_{50} >1250 μM for EGFR kinase).	5 mg
AG 17	**658425**	A selective inhibitor of the platelet-derived growth factor receptor tyrosine kinase (IC_{50} = 500 nM).	5 mg
AG 18	**658395**	An inhibitor of EGFR autophosphorylation (IC_{50} = 40 μM) and the GTPase activity of transducin (IC_{50} = 10 μM).	5 mg
AG 30	**121760**	A potent protein tyrosine kinase inhibitor that is specific for c-ErbB. Inhibits the activation of STAT5 by c-ErbB in primary erythroblasts.	5 mg
AG 43	**658450**	Useful negative control for tyrphostins (IC_{50} = 6.5 mM) for EGFR tyrosine kinase activity.	5 mg
AG 82	**658400**	A cell-permeable, competitive inhibitor of substrate binding on protein tyrosine kinases. Inhibits EGFR tyrosine kinase (IC_{50} = 3 μM) and the GTPase activity of transducin (IC_{50} = 7 μM).	5 mg
AG 99	**658430**	An inhibitor of EGFR tyrosine kinase (IC_{50} = 10 μM) and EGF-dependent cell proliferation.	5 mg
AG 112	**658440**	Inhibits EGFR tyrosine kinase (IC_{50} = 125 nM).	5 mg
AG 183	**658410**	An inhibitor of EGFR tyrosine kinase (IC_{50} = 800 nM).	5 mg
AG 213	**658405**	An inhibitor of EGFR tyrosine kinase (IC_{50} = 2.4 μM).	5 mg
AG 370	**658454**	An inhibitor of platelet derived growth factor (PDGF)-induced mitogenesis in human bone marrow fibroblasts (IC_{50} = 20 μM). Also blocks mitogenesis induced by EGF (IC_{50} = 50 μM). Inhibits PDGF receptor autophosphorylation and blocks PDGF-induced mitogenesis (IC_{50} = 20 μM).	2 mg
AG 490	**658401**	Potent inhibitor of EGFR kinase autophosphorylation (IC_{50} = 100 nM). Jak family tyrosine kinase inhibitor.	5 mg
AG 494	**658407**	Inhibitor of EGFR kinase autophosphorylation (IC_{50} = 1.24 μM) that is slightly less active than AG 555 (Cat. No. 658404).	5 mg
AG 527	**658402**	An inhibitor of EGFR kinase autophosphorylation (IC_{50} = 2.5 μM). Also inhibits the phosphorylation of poly-GAT by the EGF receptor (IC_{50} = 400 nM).	5 mg
AG 537, Bis-Tyrphostin	**658418**	Competitively inhibits EGFR kinase autophosphorylation (IC_{50} = 400 nM).	5 mg
AG 538	**658403**	A potent, competitive inhibitor of insulin-like growth factor-1 receptor (IGF-1R) kinase autophosphorylation (IC_{50} = 400 nM). Also inhibits the phosphorylation of PTK substrate poly (Glu,Tyr) by IGF-1R, IR, EGF-R, and Src (IC_{50} = 60 nM, 113 nM, and 2.4 μM respectively).	5 mg
I-OMe-AG 538	**658417**	An analog of AG 538 (Cat. No. 658403) that acts as an inhibitor of IGF-1 receptor kinase both *in vitro* and in intact cells. Inhibition is competitive with respect to the substrate binding site of IGF-1 receptor kinase. Exhibits enhanced cell-permeability and increased resistance to oxidation.	5 mg
AG 555	**658404**	A potent inhibitor of EGFR kinase autophosphorylation (IC_{50} = 700 nM). Exhibits opposite potency profiles with AG 527 (Cat. No. 658402) for EGF receptor autophosphorylation versus poly-GAT substrate phosphorylation.	5 mg
AG 556	**658415**	A selective inhibitor of EGFR kinase (IC_{50} = 5 μM) over HER1-2 kinase autophosphorylation.	5 mg
AG 592	**658406**	A selective, cell-permeable inhibitor of EGFR-tyrosine kinase activity (IC_{50} = 20.3 μM), blocks thymidine uptake in HER-14 cells, and displays anti-proliferative properties.	5 mg
AG 825	**121765**	A potent and selective inhibitor of HER-2 (*neu/erb*B-2, IC_{50} = 0.35 μM) relative to HER-1 (IC_{50} = 19 μM) autophosphorylation. The inhibition is competitive with respect to ATP binding.	2 mg
AG 835	**658409**	A less active enantiomer of AG 527 (Cat. No. 658402) that inhibits EGFR kinase poly-GAT (poly-Glu-Ala-Tyr) substrate phophorylation (IC_{50} = 860 nM).	5 mg
AG 879	**658460**	An inhibitor of nerve growth factor-dependent pp140$^{c\text{-}trk}$ tyrosine phosphorylation (EC_{50} = 10 μM). Does not affect the tyrosine phosphorylation of EGFR or PDGFR.	5 mg
AG 957	**121761**	A potent tyrosine kinase inhibitor that selectively blocks the tyrosine kinase activity of human p210$^{brc\text{-}abl}$ (K_i = 750 nM) over p140$^{bcr\text{-}abl}$ (K_i = 10 μM).	5 mg

Protein Tyrosine Kinase (PTK) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
AG 597, Adamantyl Ester	**121762**	A lipophilic, adamantyl ester form of tyrphostin AG 957 (Cat. No. 121761) that displays anti-proliferative properties. Shown to be selective and ~3 - 4 fold more potent than AG 957 as a *bcr/abl* kinase inhibitor. Also exhibits a longer serum half-life *in vivo*.	5 mg
AG 1024	**121767**	A specific inhibitor of insulin-like growth factor-1 (IGF-1) and insulin receptor kinases with significantly lower IC_{50} values for IGF-1 than for insulin receptors.	1 mg
AG 1295	**658550**	A selective inhibitor of PDGFR kinase (IC_{50} = 500 nM). Does not affect EGFR auto-phosphorylation.	5 mg
AG 1296	**658551**	More potent than AG 1295 (Cat. No. 658550). Inhibits signaling of human PDGF α-receptors (IC_{50} = 1.0 μM), β-receptors (IC_{50} = 800 nM), and the related stem cell factor receptor c-*kit* (80% inhibition at 5 μM). Has no effect on autophosphorylation of the vascular endothelial growth factor receptor KDR.	5 mg
AG 1387	**658520**	A 5-iodo analog of AG 555 (Cat. No. 628404) that is more cell-permeable than AG555. Acts as an inhibitor of protein tyrosine kinase and DNA topoisomerase I.	5 mg
AG 1433	**658553**	A potent and specific inhibitor of the PDGF β-receptor kinase (IC_{50} = 5.0 μM) and of KDR/Flk-1(IC_{50} = 9.3 μM). Also acts as an angiogenesis inhibitor.	5 mg
AG 1478	**658552**	A highly potent and specific inhibitor of the EGFR tyrosine kinase (IC_{50} = 3 nM). Inhibits the kinase activity of the closely-related HER2 (neu/*erb-B2*) receptor (IC_{50} >100 μM), the PDGFR (IC_{50} >100 μM), and $p210^{Bcr-Abl}$ (IC_{50} > 50 μM) at much higher concentrations.	5 mg
AGL 2043	**121790**	A cell-permeable, potent, selective, ATP-competitive, and reversible inhibitor of type III receptor tyrosine kinases, PDGFR (IC_{50} = 800 nM in 3T3 cells; 90 nM against purified PDGFβ-receptor), Flt3, and Kit (IC_{50} ~1 - 3 μM). Weakly inhibits PKA, EGFR, IGF-1R, VEGFR, and Src kinases (IC_{50} > 30 μM).	1 mg
NEW AGL 2263	**121850**	A cell-permeable, potent, substrate-competitive, but not ATP-competitive, inhibitor of insulin receptor kinase ((IC_{50} = 400) and insulin-like growth factor-1 receptor kinase (IC_{50} = 430 nM).	5 mg
BPDQ	**203697**	A highly potent and specific inhibitor of EGFR kinase (IC_{50} = 120 pM).	1 mg
BPIQ-I	**203696**	A highly potent and specific inhibitor of EGFR kinase (IC_{50} = 25 pM). Also inhibits $PLC\gamma_1$ at low concentrations (IC_{50} = 8 pM).	1 mg
BPIQ-II	**203704**	One of the most potent and selective inhibitors of EGFR kinase (IC_{50} = 8 pM).	1 mg
Butein	**203987**	A potent inhibitor of EGFR kinase (IC_{50} = 65 μM) and $p60^{c-src}$ (IC_{50} = 65 μM).	5 mg
CL-387, 785	**233100**	An irreversible inhibitor of autophosphorylation of EGFR (IC_{50} = 250 - 490 nM).	1 mg
Compound 56	**234505**	One of the most potent inhibitors of EGFR kinase activity (IC_{50} = 6 pM).	500 μg
Cucurbitacin I, *Cucumis sativus* L.	**238590**	A cell-permeable, potent, and highly selective inhibitor of Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway. Suppresses STAT3 tyrosine phosphorylation in v-Src-transformed NIH 3T3 cells and human lung adenocarcinoma A549 cells (IC_{50} = 500 nM).	1 mg
Curcumin, *Curcuma longa* L.	**239802**	Induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells. Inhibits the intrinsic kinase activity of EGFR.	100 mg
Daidzein	**251600**	Inactive analog of Genistein that is reported to inhibit casein kinase II activity.	25 mg
Damnacanthal	**251650**	Most potent and selective inhibitor of $p56^{lck}$ tyrosine kinase and $p56^{lck}$ autophosphorylation (IC_{50} = 17 nM). Inhibition is competitive with respect to peptide binding site and mixed non-competitive with the ATP binding site.	1 mg
Daphnetin	**268295**	A broad-spectrum inhibitor of protein kinases. Inhibits EGFR kinase (IC_{50} = 7.67 μM), PKA (IC_{50} = 9.33 μM), and PKC (IC_{50} = 25 μM).	10 mg
DMBI	**317200**	Inhibitor of the tyrosine activity of β-PDGFR (IC_{50} = 4 μM in PAC-1 cells) and FGFR1 (IC_{50} = 5 μM).	10 mg
NEW EGFR/ErbB2 Inhibitor	**324673**	A cell-permeable, potent, reversible, and ATP competitive inhibitor of EGFR and C-erbB2 (IC_{50} = 20 nM and 80 nM, respectively).	1 mg
Emodin	**324694**	Inhibitor of $p56^{lck}$ (IC_{50} = 18.5 μM). Suppresses HER2/*neu* tyrosine kinase activity in HER2/*neu* overexpressing cancer cells.	50 mg
Erbstatin Analog	**324930**	Cell-permeable stable analog of Erbstatin. Competitive inhibitor of EGFR kinase activity (IC_{50} = 780 nM). Inhibits the activation of v-Abl tyrosine kinase activity.	1 mg

Protein Tyrosine Kinase (PTK) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Geldanamycin, *Streptomyces hydroscopicus*	**345805**	Inhibitor of $p60^{c\text{-}src}$ tyrosine kinase activity. Binds Hsp90 and induces degradation of tyrosine kinases.	100 µg
Genistein	**345834**	A tyrosine kinase inhibitor that also blocks the autophosphorylation of EGFR kinase (IC_{50} = 2.6 µM). Also acts as an inhibitor of $p60^{v\text{-}src}$ (IC_{50} = 25 µM).	20 mg 50 mg
NEW GTP-14564	**371806**	A cell-permeable, potent, and specific inhibitor of class III receptor tyrosine kinases (IC_{50} = 300 nM for c-fms, c-kit, wt-FLT3 and ITD-FLT3; 1.0 µM for PDGFRβ).	5 mg
Herbimycin A, *Streptomyces* sp.	**375670**	An inhibitor of $p60^{c\text{-}src}$ (IC_{50} = 900 nM). Reversibly binds to the thiol groups of the kinase.	100 µg
HNMPA-(AM3)	**397100**	Cell-permeable inhibitor of insulin receptor tyrosine kinase (IC_{50} = 100 µM).	5 mg
JAK Inhibitor I	**420099**	A potent inhibitor of Janus Protein tyrosine Kinases (JAKs). Displays potent inhibitory activity against JAK1 (IC_{50} = 15 nM for murine JAK1), JAK2 (IC_{50} = 1 nM), JAK3 (K_i = 5 nM), and Tyk2 (IC_{50} = 1 nM).	500 µg
JAK3 Inhibitor I	**420101**	A specific inhibitor of JAK3 (IC_{50} = 78 µM). Does not affect the activity of JAK1, JAK2, ZAP/Syk, or Src tyrosine kinases.	5 mg
JAK3 Inhibitor II	**420104**	A potent, cell-permeable inhibitor of JAK3 that is reported to kill glioblastoma cells (IC_{50} = 813 nM).	5 mg
JAK3 Inhibitor III	**420106**	A potent and specific inhibitor of JAK3 (IC_{50} = 11 µM).	500 µg 1 mg
JAK3 Inhibitor IV	**420121**	A potent and selective ATP-competitive inhibitor of JAK3 with a pIC_{50} of 7.1. Weakly inhibits other tyrosine kinases (pIC_{50} = 5.6 for EGF-R; 4.4 for JAK1). In neutral buffer ($t_{1/2}$ = 36 min at 25˚C, pH 7.43), undergoes a retro-Michael breakdown to the active analog 2-naphthylvinyl ketone (Cat. No. 420122) [pIC_{50} = 6.8 for JAK3; 5.0 for EGF-R; 4.7 for JAK1].	10 mg
JAK3 Inhibitor V	**420122**	A breakdown product of JAK3 Inhibitor-IV (Cat. No. 420121) with similar inhibitory activities (pIC_{50} = 6.8 for JAK3; 5.0 for EGF-R; 4.7 for JAK1). Also inhibits STAT-5 phosphorylation and T-cell proliferation.	10 mg
NEW JAK3 Inhibitor VI	**420126**	A cell-permeable, potent inhibitor of JAK3 (IC_{50} = 27 nM). Binds to the enzyme active site and prevents IL-2-induced cellular phosphorylation of JAK3 and STAT5.	5 mg
JAK3 Inhibitor, Negative Control	**420112**	A useful negative control compound for JAK3 inhibitors.	500 µg 1 mg
Lavendustin A	**428150**	A potent inhibitor of EGFR kinase (IC_{50} = 11 nM) and $p60^{c\text{-}src}$ (IC_{50} = 500 nM).	1 mg
Lavendustin B	**428160**	Suitable for use as a negative control for Lavendustin A (IC_{50} = 1.3 µM for EGFR kinase).	1 mg
Lavendustin C	**234450**	Potent inhibitor of $p60^{c\text{-}src}$ (IC_{50} = 200 nM) and Ca^{2+}/calmodulin-dependent kinase II (IC_{50} = 200 nM).	1 mg
Lavendustin C Methyl Ester	**234455**	A potent inhibitor of EGFR kinase (IC_{50} = 600 nM).	1 mg
LFM-A11	**435301**	A useful negative control ($IC_{50} \geq 454$ µM) for LFM-A13.	500 µg 1 mg
LFM-A12	**435302**	A potent and specific inhibitor of EGFR kinase (IC_{50} = 1.7 µM).	500 µg 1 mg
LFM-A13	**435300**	A potent and specific inhibitor of Bruton's tyrosine kinase (BTK; IC_{50} = 17.2 µM for human BTK *in vitro* and IC_{50} = 2.5 µM for recombinant BTK).	5 mg
Oxindole I	**499600**	A potent and specific inhibitor of VEGFR kinase Flk-1 (IC_{50} = 390 nM).	10 mg
PD 153035	**234490**	An extremely potent and specific inhibitor of EGFR kinase activity (IC_{50} = 25 pM).	1 mg
PD 156273	**513032**	A potent inhibitor of EGFR kinase activity (IC_{50} = 690 pM).	1 mg
PD 158780	**513035**	A potent inhibitor of the EGFR tyrosine kinase activity (80 pM). Also inhibits heregulin-stimulated autophosphorylation in SK-BR-3 (IC_{50} = 49 nM) and MDA-MB-453 (IC_{50} = 52 nM) breast carcinomas.	500 µg
PD 168393	**513033**	A potent, cell-permeable, irreversible, and selective inhibitor of EGFR kinase activity (IC_{50} = 700 pM).	1 mg
PD 174265	**513040**	A potent, cell-permeable, reversible, and selective inhibitor of EGFR kinase activity (IC_{50} = 450 pM).	1 mg

Protein Tyrosine Kinase (PTK) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
PDGF Receptor Tyrosine Kinase Inhibitor I	**521230**	A cell-permeable *bis*(1H-2-indolyl)-1-methanone compound that acts as a highly selective and ATP-competitive inhibitor of PDGFR kinase (IC_{50} = 200 nM in Swiss 3T3 cells for PDGFR; 90 nM *in vitro* and 200 nM in PAE cells for PDGFβ-R; 1 μM for PDGFα-R). Also reported to inhibit Fms-like tyrosine kinase 3 (Flt3) activity (IC_{50} = 300 nM for hPDGFβ-R-mFlt3 and 100 nM in EOL-1 cells).	1 mg
PDGF Receptor Tyrosine Kinase Inhibitor II	**521231**	Prodrug form of Platelet Derived Growth Factor Receptor Tyrosine Kinase Inhibitor I (Cat. No. 521230) that acts as a highly selective, cell-permeable, ATP-competitive inhibitor of PDGFR kinase (IC_{50} = 1.1 μM, Swiss 3T3 cells). Also potently inhibits Fms-like tyrosine kinase 3 (Flt3) activity (IC_{50} = 6.2 μM for PDGFRβ-mFlt3 and 50 nM in EOL-1 cells).	1 mg
NEW PDGF Receptor Tyrosine Kinase Inhibitor III	**521232**	A cell-permeable, potent, selective, ATP-competitive inhibitor of PDGF receptor family of tyrosine kinases (IC_{50} = 50 nM for α-PDGFR; 80 nM for β-PDGFR; 50 nM for c-Kit; 230 nM for Flt3).	1 mg
Piceatannol	**527948**	Inhibitor of $p72^{Syk}$, a non-receptor tyrosine kinase (IC_{50} = 10 μM).	1 mg
PP1 Analog	**529579**	A potent, cell-permeable, and selective inhibitor of Src-family tyrosine kinases. Displays high selectivity for 1338G v-Src (IC_{50} = 1.5 nM) with respect to the wild-type v-Src (IC_{50} = 1.0 μM). Also inhibits wild-type Fyn (IC_{50} = 600 nM). Not available for sale in the USA.	1 mg
PP2	**529573**	A potent and selective inhibitor of the *Src* family of tyrosine kinases. Inhibits $p56^{lck}$ (IC_{50} = 4 nM), $p59^{fynT}$ (IC_{50} = 5 nM), and Hck (IC_{50} = 5 nM).	1 mg
PP3	**529574**	A negative control compound for PP2. Shown to inhibit EGFR kinase (IC_{50} = 2.7 μM).	1 mg
Psi-tectorigenin	**540100**	Inhibitor of EGFR kinase activity (IC_{50} = 330 nM).	500 μg
Radicicol, *Dihetero-spora chlamydosporia*	**553400**	Inhibitor of $p60^{v\text{-}src}$ kinase activity (IC_{50} = 8.2 μM). Also inhibits tyrosine phosphorylation of $p53/56^{lyn}$ in LPS-stimulated macrophages.	500 μg
$p60^{v\text{-}src}$ 137-157 Inhibitor Peptide	**657015**	Inhibitor of $p60^{v\text{-}src}$ (IC_{50} = 7.5 μM) and EGFR kinase activity.	500 μg
RG-13022	**554725**	A selective inhibitor of EGFR kinase activity. Inhibits epidermal growth factor-stimulated HER14 cell proliferation (IC_{50} = 1 μM) and tumor growth *in vivo*.	5 mg
Src Kinase Inhibitor I	**567805**	A potent, selective, dual site, competitive inhibitor of Src tyrosine kinase (IC_{50} = 44 nM and 88 nM for Src and Lck, respectively). Shown to simultaneously interact with both the ATP- and peptide-binding sites. Inhibits VEGFR2 and c-fms tyrosine kinases only at higher concentrations (IC_{50} = 320 nM and 30 μM, respectively).	1 mg
NEW Src Kinase Inhibitor II	**567806**	A potent, selective, and ATP-competitive inhibitor of Src family tyrosine kinases (IC_{50} = 1.2 μM for human recombinant Csk).	5 mg
SU4984	**572625**	Inhibitor of FGFR1 tyrosine kinase activity (IC_{50} = 10 - 20 μM in the presence of 1 mM ATP). Also inhibits aFGF-induced phosphorylation of ERK1 and ERK2 and tyrosine phosphorylation of PDGF and insulin receptors.	1 mg
SU5614	**572632**	Potent inhibitor of VEGFR kinase, Flk-1 (IC_{50} = 1.2 μM), and PDGFR kinase (IC_{50} = 2.9 μM).	1 mg
SU6656	**572635**	A potent Src family kinase inhibitor. Inhibits Src (IC_{50} = 280 nM) and closely related kinases Fyn (IC_{50} = 170 nM) and Yes (IC_{50} = 20 nM). Also inhibits Lyn (IC_{50} = 130 nM), but only weakly inhibits Lck (IC_{50} = 688 μM) and PDGFR (IC_{50} >10 μM).	1 mg
NEW Syk Inhibitor	**574711**	A cell-permeable, potent inhibitor of Syk (IC_{50} = 14 nM).	5 mg
NEW TGF-β RI Kinase Inhibitor	**616451**	A cell-permeable, potent, selective, ATP-competitive inhibitor of TGF-β RI tyrosine kinase (IC_{50} = 51 nM). Displays ~15-fold greater selectivity over p38α MAP kinase (IC_{50} = 740 nM).	5 mg
2′-Thioadenosine (PD157432)	**589400**	A potent, selective, and irreversible inhibitor of the ErbB subfamily of protein tyrosine kinases. Inactivates ErbB1 by modifying Cys^{797} at the active site. Also inhibits ErbB2 (IC_{50} = 45 μM).	2 mg
(-)-Terreic Acid, Synthetic	**581810**	A cell-permeable, selective inhibitor of Bruton's tyrosine kinase (BTK; IC_{50} = 10 μM and 3 μM for the basal and activation levels), both *in vitro* and *in vivo*.	2 mg
TX-1123	**655200**	A cell-permeable inhibitor for Src, eEF2 kinase, and PKA (IC_{50} = 2.2, 3.2, and 9.6 μM, respectively). Inhibits EGFR kinase and PKC only at much higher concentrations (IC_{50} = 320 μM).	10 mg

Protein Tyrosine Kinase (PTK) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
TX-1918	**655203**	A cell-permeable, potent inhibitor for eEF2 kinase (IC_{50} = 440 nM). Inhibits other kinases at much higher concentrations (IC_{50} = 4.4, 44, 44, and 440 μM for Src, PKA, PKC, and EGFR Kinase, respectively).	10 mg
VEGF Receptor 2 Inhibitor I	**676480**	A highly selective, cell-permeable indolin-2-one class of receptor tyrosine kinase (RTK) inhibitor (IC_{50} = 70 nm) for murine vascular endothelial growth factor receptor 2 (VEGF-R2; KDR/Flk-1). The inhibition is suggested to be competitive with respect to ATP.	1 mg
VEGF Receptor 2 Inhibitor II	**676485**	A cell-permeable receptor tyrosine kinase (RTK) inhibitor [IC_{50} = 70 nM for VEGF-R2 (KDR/Flk-1), 920 nM for PDGF-Rβ, 4.92 μM for $p60^{c\text{-}src}$, and 13.3 μM for FGF-R1]. The inhibition is suggested to be competitive with respect to ATP.	1 mg
VEGF Receptor 2 Kinase Inhibitor III (SU5416)	**676487**	A cell-permeable, selective, ATP-competitive inhibitor of VEGF-R (KDR/Flk-1) and PDGFR kinases (IC_{50} = 1 μM and 20 μM, respectively in NIH3T3 cells over-expressing Flk-1; K_m = 530 nM for ATP).	1 mg
VEGF Receptor 2 Kinase Inhibitor IV	**676489**	A potent, ATP-competitive inhibitor of the kinase activity VEGF receptor-2 (VEGFR-2; KDR/Flk-1) (IC_{50} = 19 nM). Displays ~2-fold greater selectivity for VEGFR-2 compared to platelet derived growth factor receptor β (PDGFRβ) and 10-fold selectivity compared to VEGFR-1 (Flt-1) and VEGFR-3 (Flt-4).	1 mg
VEGF Receptor 3 Kinase Inhibitor, MAZ51	**676492**	A cell-permeable, ATP-competitive inhibitor of VEGFR kinase. At low concentrations (5 μM), reported to specifically block VEGF-C and VEGF-D-induced phosphorylation of VEGFR-3, but not VEGFR-2, in PAE cells. Reported to partially block VEGFR-2 phosphorylation only at higher concentrations (50 μM).	10 mg

Src Family Protein Tyrosine Kinase Inhibitor Set

A set of 4 vials. Each set contains 20 mg of Genistein (Cat. No. 345834), 100 μg of Herbimycin A, *Streptomyces* sp. (Cat. No. 375670), and 1 mg each of PP2 (Cat. No. 529573) and PP3 (Cat. No. 529574).

Cat. No. 567816 **1 set**

Tyrosine Kinase Inhibitor Set II

A set of 4 vials. Each set contains 20 mg of Genistein (Cat. No. 345834), 1 mg of PP2 (Cat. No. 529573), 5 mg of AG 490 (Cat. No. 658401), 5 mg of AG 1296 (Cat. No. 658551), and 5 mg of AG 1478 (Cat. No. 658552).

Cat. No. 657021 **1 set**

Raf Kinase Inhibitors

Raf kinases are a group of serine/threonine kinases that include A-Raf, B-Raf, and c-Raf1. A-Raf is abundant in urogenital tissues, B-Raf is predominantly expressed in neural tissue, and C-Raf1 is ubiquitous in its distribution. Raf kinases play an important role as extracellular signal-regulating kinases in cell differentiation, proliferation, and apoptosis. The three Raf proteins share a common structure consisting of an N-terminal regulatory domain and a C-terminal kinase domain. Each Raf has three conserved regions, CR1, CR2, and CR3. In the regulatory domain, CR1 contains a Ras-binding domain and a cysteine-rich domain, CR2 is a serine/threonine-rich domain, and CR3 contains the kinase domain and is essential for Raf activity. The removal of the regulatory domain generates an oncogenic kinase.

All three Raf proteins also share common mechanisms of activation and downstream effectors. They work at the entry point of the mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) pathway, a signaling module that connects cell-surface receptors and Ras proteins to nuclear transcription factors. They serve as downstream effectors of Ras signaling; however, the interaction between Ras and Raf alone is not sufficient for full activation of Raf kinases. Additional proteins and enzymes are required for full activation. 14-3-3 proteins are known to bind directly to Raf and their binding to Ser^{621} of Raf-1 is essential to keep Raf in an inactive, but activation-competent confirmation. PKA is reported to phosphorylate Ser^{43} and Ser^{621} and prevent the activation of Raf1. Inhibition of PKA has been linked to the growth factor-induced activation of c-Raf1. Ser^{728} in the 14-3-3 binding region in B-Raf is also known to be a target for PKA phosphorylation.

Abnormal activation of Raf signaling pathway is common in several type of cancers. Hence, there is a significant interest in the development of specific inhibitors that may reverse the progression of these tumors. These inhibitors may block the expression of Raf protein, block its interaction with Ras, or block its kinase activity.

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Raf Kinase Inhibitors

Product	Cat. No.	Comments	Size
Raf1 Kinase Inhibitor I	**553008**	A potent c-Raf1 kinase inhibitor (IC_{50} = 9 nM). Shows ≥ 100-fold selectivity for Raf kinase versus Cdk1, Cdk2, *c-src*, ERK2, MEK, p38, Tie2, VEGFR2 and *c-fms*.	1 mg
Raf1 Kinase Inhibitor II	**553011**	A cell-permeable potent inhibitor of Raf1 kinase (IC_{50} = 12 nM).	1 mg
ZM 336372	**692000**	A potent, specific, and competitive inhibitor of c-Raf (IC_{50} = 70 nM). Inhibits c-Raf with ten-fold greater potency compared to B-Raf. Has no significant effect on many other protein kinases tested (even at 50 μM) with the exception of SAPK2α/p38α (IC_{50} = 2 μM) and SAPK2β/p38β2 (IC_{50} = 2 μM).	1 mg

Rho Kinase (ROCK) Inhibitors

Rho kinase (ROCK), a serine/threonine kinase, serves as a target protein for small GTP-binding protein Rho. It serves as an important mediator of numerous cellular functions, including focal adhesions, motility, smooth muscle contraction, and cytokinesis. In smooth muscle, ROCK plays an important role in Ca^{2+} sensitization and the control of vascular tone. It modulates the level of phosphorylation of the myosin II light chain of myosin II, mainly through inhibition of myosin phosphatase, and contributes to agonist-induced Ca^{2+} sensitization in smooth muscle contraction.

Rho kinase is found in two forms, ROCK 1 (ROCKβ; p160-ROCK) and ROCK 2 (ROCKα). Both ROCK 1 and ROCK 2 contain an amino-terminal catalytic kinase domain, a central coiled-coil domain of about 600 amino acids, and a carboxyl-terminal pleckstrin homology (PH) domain that is split by a cysteine-rich region. Rho/GTP interacts with the C-terminal portion of the central coiled-coil domain and activates the kinase activity of ROCK. Since the ROCK-mediated pathway plays important roles in vascular smooth muscle contraction, cell adhesion, and cell motility, it has gained importance in the pathogenesis of atherosclerosis. ROCK inhibitors are shown to suppress coronary artery spasms. A long-term inhibition of ROCK is reported to block the development of coronary arteriosclerotic lesions.

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Rho Kinase (ROCK) Inhibitors

Product	Cat. No.	Comments	Size
HA 1077, Dihydrochloride	**371970**	A cell-permeable Ca^{2+} antagonist that inhibits Rho-associated kinase, PKA (IC_{50} = 1.6 μM), PKG (IC_{50} = 1.6 μM), and MLCK (IC_{50} = 3.6 μM).	1 mg
Rho-Kinase Inhibitor	**555550**	A cell-permeable, highly specific, potent, and ATP-competitive inhibitor of G-protein Rho-associated kinase (ROCK; K_i = 1.6 nM).	1 mg
NEW Rho-Kinase Inhibitor II	**555551**	A potent, selective, and ATP-competitive inhibitor of Rho-associated protein kinase (ROCK; IC_{50} = 200 nM).	5 mg
Y-27632	**688000**	A highly potent, cell-permeable, selective inhibitor of Rho-associated protein kinase (K_i = 140 nM for $p160^{ROCK}$). Also inhibits ROCK-II with almost equal potency. Inhibition is competitive with respect to ATP.	1 mg 5 mg
Y-27632 in Solution	**688001**	A 5 mM solution of Y-27632 (Cat. No. 688000) in H_2O.	500 μg

NEW! Sphingosine Kinase Inhibitor

(2-(*p*-Hydroxyanilino)-4-(*p*-chlorophenyl) thiazole)

A cell-permeable, potent, non-ATP-competitive, and highly specific inhibitor of sphingosine kinase (IC_{50} = 500 nM for GST-hSK).

Cat. No. 567731 **10 mg**

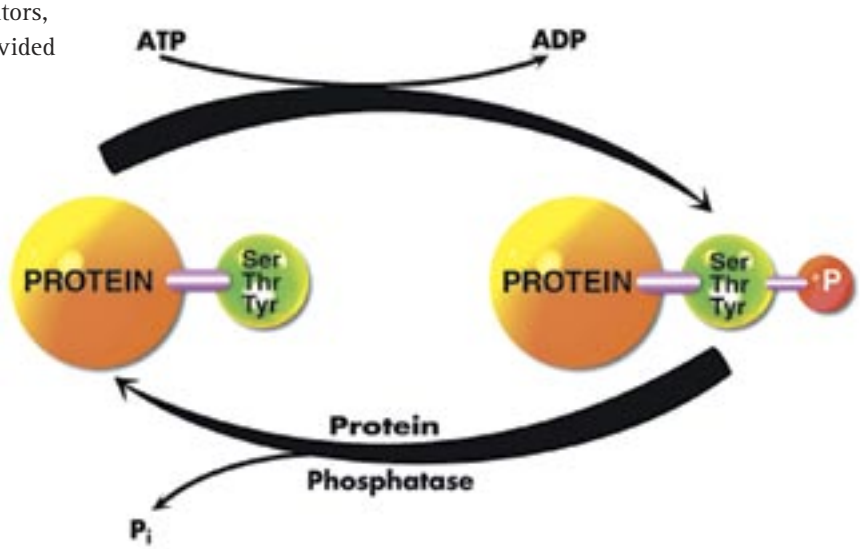
Protein Phosphatase Inhibitors

Phosphorylation and dephosphorylation of structural and regulatory proteins are major intracellular control mechanisms in eukaryotes. Protein kinases transfer a phosphate from ATP to a specific protein, typically at serine, threonine, or tyrosine residues. Phosphatases remove the phosphoryl group and restore the protein to its original dephosphorylated state. Hence, the phosphorylation-dephosphorylation cycle can be regarded as a molecular "on-off" switch.

Protein phosphatases (PPs) have been classified into three distinct categories: serine/threonine (Ser/Thr)-specific, tyrosine-specific, and dual-specificity phosphatases. Based on biochemical parameters, substrate specificity, and sensitivity to various inhibitors, Ser/Thr protein phosphatases are divided into two major classes. Type I phosphatases, which include PP1, can be inhibited by two heat-stable proteins known as Inhibitor-1 (I-1) and Inhibitor-2 (I-2). They preferentially dephosphorylate the β-subunit of phosphorylase kinase. Type II phosphatases are subdivided into spontaneously active (PP2A), Ca^{2+}-dependent (PP2B), and Mg^{2+}-dependent (PP2C) classes of phosphatases. They are insensitive to heat-stable inhibitors and preferentially dephosphorylate the α-subunit of phosphorylase kinase.

Protein tyrosine phosphatases (PTPs) are relatively recent additions to the phosphatase family. They remove phosphate groups from phosphorylated tyrosine residues of proteins. PTPs display diverse structural features and play important roles in the regulation of cell proliferation, differentiation, cell adhesion and motility, and cytoskeletal function. They are either transmembrane receptor-like PTPs or cytosolic enzymes. Each PTP contains a highly conserved catalytic domain of about 240 residues that contains highly conserved arginine and cysteine residues at the catalytic domain. The diversity of PTPs is primarily due to the variety of non-catalytic regulatory sequences and targeting domains attached to both N- and C-termini.

Another category of protein phosphatases is the dual-specificity phosphatases (DSP), which play a key role in the dephosphorylation of MAP kinases. Hence, they are also termed as MAP kinase phosphatases (MKPs). On the basis of predicted structures, MKPs have been divided into three subgroups. Group I contains DSP1, DSP2, DSP4, and DSP5; group II enzymes are DSP6, DSP7, DSP9, and DSP10; and group III consists of DSP8 and DSP16. All the DSPs share strong amino-acid sequence homology in their catalytic domains. The catalytic domain contains a highly conserved consensus sequence $\underline{D}X_{26}$(V/L)X(V/I)H$\underline{C}$XAG(I/V) S$\underline{R}$SXT(I/V)XXAY(L/I)M, where X could be any amino acid. The three underlined amino acids are reported to be essential for the catalytic activity of



DSPs. The cysteine is required for the nucleophilic attack on the phosphorus of the substrate and the formation of the thiol-phosphate intermediate. The conserved arginine binds the phosphate group of phospho-tyrosine or phospho-threonine, enabling transition-state stabilization, and the aspartate enhances catalysis by protonating oxygen on the departing phosphate group.

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Protein Phosphatase Inhibitors

Product	Cat. No.	Comments	Size
bpV(bipy)	**203694**	A potent protein tyrosine phosphatase (PTP) inhibitor (K_i = 100 nM for insulin receptor dephosphorylation).	5 mg
bpV(HOpic)	**203701**	A potent protein tyrosine phosphatase (PTP) inhibitor.	5 mg
bpV(phen)	**203695**	A potent protein tyrosine phosphatase (PTP) inhibitor. Exhibits 1000-fold potency over sodium orthovanadate.	10 mg
bpV(pic)	**203705**	A potent protein tyrosine phosphatase (PTP) inhibitor.	5 mg
Calcineurin Autoinhibitory Peptide	**207000**	A specific calcineurin inhibitor (PP2B) (IC_{50} = 10 μM).	250 μg
NEW Calcineurin Autoinhibitory Peptide, Cell-permeable	**207001**	A cell-permeable peptide composed of the calcineurin (CaN) autoinhibitory domain (AID) fused to a poly-arginine-based protein transduction domain (11R) that inhibits CaN phosphatase activity.	1 mg
Calyculin A	**208851**	A cell-permeable phosphorylated polyketide that inhibits PP2A ~ PP1 >> PP2B (IC_{50} for PP2A = 0.5 -1.0 nM and for PP1 = 2.0 nM).	10 μg
Cantharidic Acid	**210150**	A terpenoid compound with high selectivity for PP2A (IC_{50} = 50 nM).	10 mg
Cantharidin	**210155**	A cell-permeable terpenoid that inhibits PP2A > PP1 >> PP2B (IC_{50} for PP2A = 40 nM and for PP1 = 473 nM).	20 mg
Cyclosporin A	**239835**	Binds to cyclophilin in cells; the complex inhibits PP2B with nanomolar affinity.	100 mg
Cypermethrin	**239900**	A potent inhibitor of PP2B (IC_{50} = 40 pM).	10 mg
DARPP-32	**251755**	A potent inhibitor of PP1 (IC_{50} = 1 - 2 μM).	100 μg
DARPP-32, Phospho-	**251756**	A potent inhibitor of PP1 (IC_{50} = 1 nM).	30 μg
Deltamethrin	**253300**	A potent inhibitor of PP2B (IC_{50} = 100 pM).	10 mg
Dephostatin	**263200**	A protein tyrosine phosphatase (PTP) inhibitor (IC_{50} = 7.7 μM).	1 mg
3,4-Dephostatin	**263202**	A protein tyrosine phosphatase inhibitor (IC_{50} = 18 μM).	1 mg
3,4-Dephostatin, Ethyl-	**263203**	A more stable ethyl analog of the protein tyrosine phosphatase (PTP) inhibitor 3,4-Dephostatin (Cat. No. 263202). Potently inhibits PTP1B (IC_{50} = 3.18 μM).	1 mg
1,4-Dimethylendothall	**311250**	A useful negative control for Canthardic Acid (Cat. No. 210150), Canthardin (Cat. No. 210155), and Endothall (Cat. No. 324760).	10 mg
DMHV	**322130**	A potent, cell-permeable, and reversible PTP inhibitor.	10 mg
Endothall	**324760**	A specific inhibitor of PP2A (IC_{50} = 90 nM).	20 mg
Fenvalerate	**341380**	A potent inhibitor of PP2B (IC_{50} = 2 - 4 nM).	25 mg
Fostriecin, Sodium Salt *Streptomyces bulveraceous*	**344280**	A potent PP2A inhibitor (IC_{50} = 3.2 nM). Inhibits PP1 only at higher concentrations (IC_{50} = 131 μM).	10 μg
Microcystin-LF	**475814**	A more cell-permeable analog of Microcystin-LR (Cat. No. 475815). Useful for studies in intact cells.	25 μg
Microcystin-LR	**475815**	A cyclic peptide that inhibits PP2A~ PP1 >> PP2B (IC_{50} for PP2A = 40 pM and for PP1 = 1.7 nM). Does not enter some mammalian cells.	500 μg
Microcystin-LW	**475818**	A more cell-permeable analog of Microcystin-LR (Cat. No. 475815). Useful for studies in intact cells.	25 μg
Microcystin-RR	**475816**	A cyclic peptide that inhibits PP2A~ PP1 >> PP2B (IC_{50} = 1.4 μM). Does not enter some mammalian cells.	250 μg
mpV(pic)	**475950**	A potent PTP inhibitor. More potent for insulin receptor (IR) dephosphorylation than EGFR dephosphorylation.	10 mg
α-Naphthyl Acid Phosphate	**479775**	A broad-spectrum protein phosphatase inhibitor.	5 g
NIPP-1, His•Tag™, Bovine Thymus, Recombinant, *E. coli*	**482251**	A potent and specific inhibitor or protein phosphatase 1 (PP1; K_i = 1 - 10 pM) that can be used to distinguish PP1 from other major serine/threonine protein phosphatases, including PP2A, PP2B, and PP2C.	1 μg
Okadaic Acid	**495604**	A cell-permeable inhibitor of PP2A > PP1 >> PP2B. (IC_{50} for PP2A = 100 pM; for PP1 = 10 -15 nM; and for PP2B = 5 μM).	10 μg 25 μg 100 μg

Protein Phosphatase Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Okadaic Acid, Ammonium Salt	**459616**	A water-soluble form of Okadaic Acid (Cat. No. 495604). Inhibits protein phosphatases 1 and 2A.	25 µg
Okadaic Acid, Potassium Salt	**459618**	A water-soluble form of Okadaic Acid (Cat. No. 495604). Inhibits protein phosphatases 1 and 2A.	50 µg
Okadaic Acid, Sodium Salt	**459620**	A water-soluble form of Okadaic Acid (Cat. No. 495604). Inhibits protein phosphatases 1 and 2A.	25 µg
Protein Phosphatase Inhibitor 2, Rabbit Muscle, Recombinant	**539516**	Inhibits the catalytic subunit of PP1 (IC_{50} = 2 nM).	20 µg
Protein Phosphatase 2A Inhibitor I_1^{PP2A}, Human, Kidney, Recombinant, *E. coli*	**539552**	Potently inhibits all forms of PP2A (K_i = ~100 pM).	250 ng
Protein Phosphatase 2A Inhibitor I_2^{PP2A}, Human, Recombinant, *E. coli*	**539620**	Potently inhibits PP2A (K_i = ~100 pM).	250 ng
Protein Tyrosine Phosphatase Inhibitor I	**540200**	A potent, cell-permeable, covalent PTP inhibitor.	10 mg
Protein Tyrosine Phosphatase Inhibitor II	**540205**	A potent, cell-permeable, covalent PTP inhibitor.	25 mg
Protein Tyrosine Phosphatase Inhibitor III	**540210**	A potent, cell-permeable, covalent PTP inhibitor.	10 mg
Protein Tyrosine Phosphatase Inhibitor IV	**540211**	A potent, reversible, substrate competitive, active-site-directed inhibitor of protein tyrosine phosphatases (PTP). Reported to inhibit SHP-2 (IC_{50} = 1.8 µM), PTP1B (IC_{50} = 2.5 µM), PTP-ε (IC_{50} = 8.4 µM), PTP-Meg-2 (IC_{50} = 13 µM), PTP-σ (IC_{50} = 20 µM), PTP-β (IC_{50} = 6.4 µM), and PTP-µ (IC_{50} = 6.7 µM).	10 mg
Protein Tyrosine Phosphatase CD45 Inhibitor	**540215**	A cell-permeable pivalamide with a 9,10-phenanthrenedione core that displays antiproliferative properties. Acts as a potent, selective, competitive, and reversible inhibitor of CD45 (IC_{50} = 200 nM using *p*NPP as the substrate, 3.8 µM for CD45 *lck*, > 30 µM for PTP1B *lck*).	1 mg
RK-682	**557322**	A specific non-cell-permeable inhibitor of PTP. Inhibits dephosphorylation activity of CD45 (IC_{50} = 54 µM) and VHR (IC_{50} = 2.0 µM) *in vitro*.	200 µg
Sodium Orthovanadate	**567540**	Inhibitor of protein tyrosine phosphatases of general/broad specificity; potent inhibitor of alkaline phosphatase.	5 g
Sodium Stibogluoconate	**567565**	An irreversible inhibitor of (PTPase), including Src homology PTPase-1 (SHP-1). Exhibits anti-leishmanial properties. At higher concentrations, inhibits SHP-2 and PTP1B activities.	1 g
Suramin, Sodium Salt	**574625**	Useful as a reversible and competitive inhibitor of protein tyrosine phosphatases.	50 mg 200 mg
Tautomycin	**580551**	A potent inhibitor of PP1 (IC_{50} = 1 nM), PP2A (IC_{50} = 10 nM), and smooth muscle endogenous phosphatase (IC_{50} = 6 nM).	50 µg

Phosphatase Inhibitor Cocktail Set I

A cocktail of three inhibitors of alkaline phosphatases and serine/threonine protein phosphatases such as PP1 and PP2A. Each vial contains 2.5 mM (-)-*p*-Bromotetramisole Oxalate, 500 µM Cantharidin (Cat. No. 210155), and 500 nM Microcystin-LR (Cat. No. 475815). Note: 1 set = 5 x 1 ml.

Cat. No. 524624 **1 set**

Phosphatase Inhibitor Cocktail Set II

A cocktail of five inhibitors of acid and alkaline phosphatases as well as protein tyrosine phosphatases. Suitable for use with tissue and cell extracts, including extracts containing detergents. Each vial contains 200 mM Imidazole, 100 mM Sodium Fluoride, 115 mM Sodium Molybdate, 100 mM Sodium Orthovanadate, and 400 mM Sodium Tartrate Dihydrate. Dilute 1:100 just prior to use.
Note: 1 set = 5 x 1 ml.

Cat. No. 524625 **1 set**

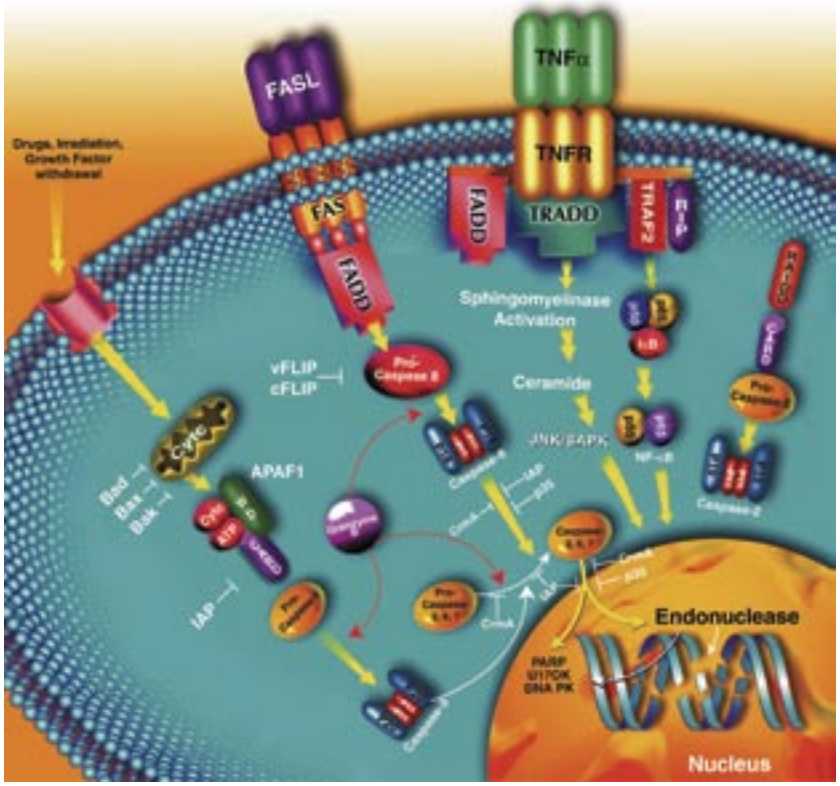
Apoptosis

Caspase Inhibitors

Activation of caspases is one of the most widely recognized features of apoptosis. Caspases are cysteine-dependent, aspartate-specific proteases. They exist as latent precursors, which, when activated, initiate the death program by destroying key components of the cellular infrastructure and activating factors that mediate damage to the cells. Thus far, 14 members of the caspase family have been identified, 11 of which are present in humans. Caspases have been categorized into upstream initiators and downstream executioners. A distinctive feature of caspases is the absolute requirement of an aspartic acid residue in the substrate P_1 position. The P_4 residue is important in substrate recognition and specificity. Generally, catalysis involves a cysteine protease mechanism. The tetrapeptide corresponding to the substrate P_4 - P_1 residues is sufficient to recognize both caspase-1 and caspase-3. This also forms the basis of designing novel inhibitors of caspases.

Caspase activation is generally considered as the "point of no return" in apoptotic pathways. Caspases are activated via two major pathways: the receptor-mediated (Fas ligand or TNFα-mediated) pathway and the mitochondrial pathway. The receptor-mediated pathway leads to the activation of pro-caspase-8. In the mitochondrial pathway pro-apoptotic members of the Bcl-2 family associate with mitochondria and direct the release of cytochrome *c* (Cyt *c*) and other proteins, which activate pro-caspase-9.

Caspase inhibitors act by binding to the active site of caspases either in a reversible or irreversible manner. Inhibitor design includes a peptide recognition sequence attached to a functional group such as an aldehyde (CHO), chloromethylketone (CMK), or fluoromethylketone (FMK). The peptide recognition sequence corresponding to that found in endogenous substrates determines the specificity of a particular caspase. For example, compounds with the Ac-YVAD-CHO sequence are potent inhibitor of caspases-1 ($K_i \approx 10$ nM), and exhibit very weak inhibitory effect on caspases-3 and -7 ($K_i \geq 50$ μM). Exclusion of the tyrosine residue from the inhibitor peptide results in a potent but less specific inhibitor, for example; Z-VAD-FMK inhibits not only caspases-1 and -4, but also caspases-3 and -7.



Caspase Inhibitors

Product	Cat. No.	Sequence	Cell-permeable?	Reversible?	Known Target Caspases (or Granzyme B)	Size
Caspase Inhibitor I	**627610**	Z-VAD(OMe)-FMK[a]	Yes	No	General	1 mg
Caspase Inhibitor I, Biotin Conjugate	**218742**	Biotin-X-VAD(OMe)-FMK[a]	–	No	General	1 mg
Caspase Inhibitor II	**218735**	Ac-VAD-CHO‡	No	Yes	General	1 mg
Caspase Inhibitor II, Cell-Permeable	**218830**	Ac-AAVALLPAVLLALLAPVAD-CHO	Yes	Yes	General	1 mg
Caspase Inhibitor III	**218745**	Boc-D(OMe)-FMK[a]	Yes	No	General	250 µg 1 mg
Caspase Inhibitor IV	**218784**	Boc-D(OBzl)-CMK[b]	Yes	No	General	5 mg
Caspase Inhibitor VI	**219007**	Z-VAD-FMK[a]	–	No	General	250 µg 1 mg
Caspase Inhibitor VIII	**218729**	Ac-VDVAD-CHO	No	Yes	2, 3, 7	1 mg
Caspase Inhibitor, Negative Control	**342000**	Z-FA-FMK	Yes	No	1	1 mg 5 mg
Caspase-1 Inhibitor I	**400010**	Ac-YVAD-CHO‡	No	Yes	1, 4	1 mg 5 mg
Caspase-1 Inhibitor I, Cell-permeable	**400011**	Ac-AAVALLPAVLLALLAP-YVAD-CHO	Yes	Yes	1, 4	1 mg
Caspase-1 Inhibitor II	**400012**	Ac-YVAD-CMK[b]	Yes	No	1, 4	5 mg
Caspase-1 Inhibitor II, Biotin Conjugate	**400022**	Biotin-YVAD-CMK[b]	–	No	1, 4	5 mg
Caspase-1 Inhibitor III, Biotin Conjugate	**400024**	Biotin-YVAD-FAOM[c]	–	No	1, 4	5 mg
Caspase-1 Inhibitor IV	**400015**	Ac-YVAD-AOM[d]	Yes	No	1, 4	1 mg
Caspase-1 Inhibitor V	**400019**	Z-Asp-CH_2-DCB[e]	Yes	No	1, 4	5 mg
Caspase-1 Inhibitor VI	**218746**	Z-YVAD(OMe)-FMK[a]	Yes	No	1, 4	250 µg 1 mg
Caspase-1 Inhibitor VIII	**218727**	Ac-WEHD-CHO	No	Yes	1, 8	500 µg
Caspase-2 Inhibitor I	**218744**	Z-VD(OMe)VAD(OMe)-FMK[a]	Yes	No	2	250 µg 1 mg
Caspase-2 Inhibitor II	**218814**	Ac-LDESD-CHO	No	Yes	2, 3	1 mg 5 mg
Caspase-3 Inhibitor I	**235420**	Ac-DEVD-CHO‡	No	Yes	3, 6, 7, 8, 10	1 mg 5 mg
Caspase-3 Inhibitor I, Biotin Conjugate	**235422**	Biotin-DEVD-CHO‡	–	Yes	3, 6, 7, 8, 10	1 mg
Caspase-3 Inhibitor I, Cell-Permeable	**235423**	Ac-AAVALLPAVLLALLAP-DEVD-CHO	Yes	Yes	3, 6, 7, 8, 10	1 mg
Caspase-3 Inhibitor I, Cell-Permeable, in Solution	**235427**	Ac-AAVALLPAVLLALLAP-DEVD-CHO	Yes	Yes	3, 6, 7, 8, 10	1 mg
Caspase-3 Inhibitor II	**264155**	Z-D(OMe)E(OMe)VD(OMe)-FMK[a]	Yes	No	3, 6, 7, 8, 10	250 µg 1 mg
Caspase-3 Inhibitor II, in Solution	**264156**	Ac-AAVALLPAVLLALLAP-DEVD-CHO	Yes	Yes	3, 6, 7, 8, 10	250 µg
Caspase-3 Inhibitor II, Biotin Conjugate	**218747**	Biotin-X-D(OMe)E(OMe)VD(OMe)-FMK[a]	–	No	3, 6, 7, 10	1 mg
Caspase-3 Inhibitor III	**218750**	Ac-DEVD-CMK[b]	Yes	No	3, 6, 7, 8, 10	1 mg 5 mg
Caspase-3 Inhibitor IV	**235421**	Ac-DMQD-CHO‡	No	Yes	3	1 mg 5 mg
Caspase-3 Inhibitor V	**219002**	Z-D(OMe)QMD(OMe)-FMK	Yes	No	3	1 mg

Key a: FMK = Fluoromethyl ketone; b: CMK = Chloromethyl ketone; c: FAOM = 2,6-bis(trifluoromethyl) benzoyloxymethyl ketone; d: AOM = 2,6-dimethylbenzoyloxy ketone; e: DCB = 2,6-dichlorobenzoyloxy; ‡: These aldehyde-based inhibitors may be cell-permeable, albeit to a lesser extent.

Caspase Inhibitors, *continued*

Product	Cat. No.	Sequence	Cell-permeable?	Reversible?	Known Target Caspases (or Granzyme B)	Size
Caspase-3/7 Inhibitor I	**218826**	–	Yes	Yes	3, 7	1 mg
Caspase-4 Inhibitor I	**218755**	Ac-LEVD-CHO‡	No	Yes	4	1 mg
Caspase-4 Inhibitor I, Cell-Permeable	**218766**	Ac-AAVALLPAVLLALLAP-LEVD-CHO	Yes	Yes	4	1 mg
Caspase-5 Inhibitor I	**218753**	Z-WE(OMe)HD(OMe)-FMK[a]	Yes	No	1, 4, 5	250 µg 1 mg
Caspase-6 Inhibitor I	**218757**	Z-VE(OMe)ID(OMe)-FMK[a]	Yes	No	6	250 µg 1 mg
Caspase-6 Inhibitor II	**218758**	Ac-VEID-CHO‡	No	Yes	6	5 mg
Caspase-6 Inhibitor II, Cell-Permeable	**218767**	Ac-AAVALLPAVLLALLAP-VEID-CHO	Yes	Yes	6	1 mg
Caspase-8 Inhibitor I (Granzyme B Inhibitor II)	**368055**	Ac-IETD-CHO‡	No	Yes	8, Granzyme B	1 mg
Caspase-8 Inhibitor I, Cell-permeable	**218773**	Ac-AAVALLPAVLLALLAP-IETD-CHO	Yes	Yes	8, Granzyme B	1 mg
Caspase-8 Inhibitor II (Granzyme B Inhibitor III)	**218759**	Z-IE(OMe)TD(OMe)-FMK[a]	Yes	No	8, Granzyme B	250 µg 1 mg
Caspase-9 Inhibitor I	**218761**	Z-LE(OMe)HD(OMe)-FMK[a]	Yes	No	9	250 µg 1 mg
Caspase-9 Inhibitor II, Cell-Permeable	**218776**	Ac-AAVALLPAVLLALLAP-LEHD-CHO	Yes	Yes	9	1 mg
Caspase-9 Inhibitor III	**218728**	Ac-LEHD-CMK	Yes	No	9	1 mg
Caspase-13 Inhibitor I	**219005**	Ac-LEED-CHO‡	No	Yes	13	1 mg
Caspase-13 Inhibitor II	**219009**	Z-LE(OMe)E(OMe)D(OMe)-FMK[a]	Yes	No	13	250 µg 1 mg
Crm A Recombinant	**PF122**	–	No	–	1, Granzyme B	100 µg
Granzyme B Inhibitor I	**368050**	Z-AAD-CMK[b]	Yes	No	Granzyme B	1 mg
Granzyme B Inhibitor IV	**368056**	Ac-IEPD-CHO	No	Yes	8, Granzyme B	1 mg
Group III Caspase Inhibitor I	**368620**	Z-A-E(OMe)-V-D(OMe)-FMK[a]	Yes	No	6, 8, 9, 10	1 mg
Group III Caspase Inhibitor II	**368625**	Ac-AEVD-CHO‡	No	Yes	6, 8, 9, 10	1 mg
Q-VD-Oph, Non-O-methylated	**551476**	Q-Val-Asp-CH2-Oph	Yes	No	3, 8, 9, 10, 12	1 mg
XIAP, Human, Recombinant, *E. coli*	**PF137**	–	No	–	3, 7	50 µg

Key a: FMK = Fluoromethyl ketone; b: CMK = Chloromethyl ketone; c: FAOM = 2,6-bis(trifluoromethyl) benzoyloxymethyl ketone; d: AOM = 2,6-dimethylbenzoyloxy ketone; e: DCB = 2,6-dichlorobenzoyloxy; ‡: These aldehyde-based inhibitors may be cell-permeable, albeit to a lesser extent.

Granzyme Inhibitors

Granyme Inhibitors

Product	Cat. No.	Comments	Size
Caspase-8 Inhibitor I, Cell-Permeable	**218773**	A potent, cell-permeable and reversible inhibitor of caspase-8 (FLICE, MACH, Mch5) and Granzyme B.	1 mg
Caspase-8 Inhibitor II in Solution	**218840**	A 5 mM solution of Caspase-8 Inhibitor I, Cell-Permeable (Cat. No. 218773) in anhydrous DMSO.	250 µg
Caspase-8 Inhibitor II (Granzyme B Inhibitor III)	**218759**	A potent, cell-permeable, irreversible inhibitor of caspase-8 and Granzyme B.	250 µg 1 mg
Crm A Recombinant	**PF122**	An inhibitor of caspase-1 and Granzyme B.	100 µg
Granzyme B Inhibitor I	**368050**	A weak inhibitor of the human and murine Granzyme B. Also inhibits the apoptosis related DNA fragmentation in lymphocytes by fragmentin 2, a rat lymphocyte granule protease homologous to Granzyme B (ID_{50} = 300 nM).	1 mg
Granzyme B Inhibitor II	**368055**	A potent, reversible inhibitor of Granzyme B and caspase-8.	1 mg
Granzyme B Inhibitor IV	**368056**	A reversible inhibitor of Granzyme B that also inhibits caspase-8.	1 mg

Caspase Inhibitor Set I

The set of 3 separate vials. Each set contains 1 mg of Caspase-3 Inhibitor II, Z-DEVD-FMK (Cat. No. 264155); Caspase-1 Inhibitor I, Ac-YVAD-CHO (Cat. No. 400010); and Caspase Inhibitor I, Z-VAD-FMK (Cat. No. 627610).

Cat. No. 235429 **1 set**

Caspase Inhibitor Set II

The set of 8 separate vials. Each set contains 250 µg of Caspase-1 Inhibitor VI, Z-YVAD-FMK (Cat. No. 218746); Caspase-2 Inhibitor I, Z-VDVAD-FMK (Cat. No. 218744); Caspase-3 Inhibitor II, Z-DEVD-FMK (Cat. No. 264155); Caspase-5 Inhibitor I, Z-WEHD-FMK (Cat. No. 218753); Caspase-6 Inhibitor I, Z-VEID-FMK (Cat. No. 218757); Caspase-8 Inhibitor II, Z-IETD-FMK (Cat. No. 218759); Caspase-9 Inhibitor I, Z-LEHD-FMK (Cat. No. 218761); and Caspase Inhibitor III, Boc-D-FMK (Cat. No. 218745).

Cat. No. 218772 **1 set**

Caspase Inhibitor Set III

A set of 8 separate vials. Each set contains a ready-to-use DMSO solution of irreversible inhibitors of various members of the caspase-family proteases. Contains 25 µl (2 mM) each of Caspase-1 Inhibitor VI, Z-YVAD-FMK (Cat. No. 218746); Caspase-2 Inhibitor I, Z-VDVAD-FMK (Cat. No. 218744); Caspase-3 Inhibitor II, Z-DEVD-FMK (Cat. No. 264155); Caspase-5 Inhibitor I, Z-WEHD-FMK (Cat. No. 218753); Caspase-6 Inhibitor I, Z-VEID-FMK (Cat. No. 218757); Caspase-8 Inhibitor II, Z-IETD-FMK (Cat. No. 218759); Caspase-9 Inhibitor I, Z-LEHD-FMK (Cat. No. 218761); and Caspase Inhibitor I, Z-VAD-FMK (Cat. No. 627610).

Cat. No. 218806 **1 set**

Caspase Inhibitor Set IV

A set of 6 separate vials. Each set contains a ready-to-use solution of reagents for caspase inhibition studies and an apoptosis inducer. Contains 25 µl of a 10 mM solution in DMSO of Caspase-3 Inhibitor II, Z-DEVD-FMK (Cat. No. 264155); Caspase-8 Inhibitor II, Z-IETD-FMK (Cat. No. 218759); Caspase-9 Inhibitor I, Z-LEHD-FMK (Cat. No 218761); general caspase inhibitor, Z-VAD-FMK (Cat. No. 627610); the negative control Z-FA-FMK (Cat. No. 342000), and an aqueous solution (100 µl, 10.5 µM) of an apoptosis inducer, Doxorubicin, Hydrochloride (Cat. No. 324380).

Cat. No. 218825 **1 set**

Other Inhibitors of Apoptosis

Other Inhibitors of Apoptosis

Product	Cat. No.	Comments	Size
Apoptosis Inhibitor (M50054)	**178488**	A cell-permeable inhibitor of apoptosis induction (IC_{50} = 283 μM in FasL-stimulated WC8 cells, 550 μM in etoposide-stimulated U937 cells). The anti-apoptotic effects are attributable to the inhibition of caspase-3 activation (IC_{50} = 334 μM in etoposide-stimulated U937 cells).	10 mg
NEW Apoptosis Inhibitor II, NS3694	**178494**	A cell-permeable compound that specifically prevents the active ~700-kDa apoptosome complex formation triggered by cytochrome c release. Protects against apoptosome-mediated caspase activation and cell death.	10 mg
Bax-Inhibiting Peptide, V5	**196810**	A cell-permeable pentapeptide based on the Ku70-Bax inhibiting domain that offers cytoprotection. Functions as effectively as the Caspase Inhibitor VI (Z-VAD-FMK; Cat. No. 219007) for Bax-mediated apoptosis (~50 - 200 μM).	5 mg
Bax-Inhibiting Peptide, Negative Control	**196811**	A cell-permeable mutated analog of the Bax-Inhibiting Peptide, V5 (Cat. No. 196810) that serves as a negative control. Does not suppress Bax-mediated apoptosis (~200 μM).	5 mg
NEW Fas/FasL Antagonist, Kp7-6	**341291**	Specifically antagonizes Fas/FasL-mediated cellular apoptotic signals (58% reduction of FasL-induced apoptosis in Jurkat cells at 1 mg/ml). Binds to FasL (Cat. Nos. PF033 and PF092) and Fas (CD95/APO-1) with comparable affinity (K_d = 11.2 & 13.2 μM, respectively).	25 mg
Humanin, Human, Synthetic	**400140**	An anti-apoptotic peptide that when expressed intracellularly, offers protection against neuronal apoptosis induced by presenilin and APP mutants associated with familial Alzheimer's disease (AD). Reduces cytochrome c release *in vitro* by directly binding to Bax (K_d ~2 nM).	1 mg
Pifithrin-α	**506132**	A cell-permeable chemical inhibitor of p53. Reversibly inhibits p53-dependent transactivation of p53-responsive genes and reversibly blocks p53-mediated apoptosis.	5 mg 10 mg
Pifithrin-α, Cyclic-	**506134**	A cell-permeable and very stable analog of Pifithrin-α (Cat. No. 506132) with similar biological function, but with reduced cytotoxicity. Reversibly blocks p53-mediated apoptosis.	10 mg

Delegating Authority.

Cell Division/Cell Cycle/Cell Adhesion

Cell Adhesion Inhibitors

Cell adhesion is crucial in the formation and maintenance of coherent multi-cellular structures. Two major types of cell adhesion processes are seen in multi-cellular organisms: cell-cell adhesion where physical bonds are formed between adjacent cells, and cell-matrix adhesion where cells bind to adhesive proteins in the extracellular matrix (ECM). A wide variety of adhesion molecules have been identified that fall into four major families: cadherins, immunoglobulin (Ig)-like adhesion molecules, integrins, and selectins.

Cadherins are the main mediators of Ca^{2+}-dependent cell-cell adhesion. Cadherin-mediated cell-cell adhesion is accomplished by homophilic protein-protein interactions between two cadherin molecules on cell surface. This interaction is mediated by interactions between the His-Ala-Val domains and between Trp residues and hydrophobic pockets in amino-terminal cadherin domains. Cadherins are critical in segregating embryonic cells into tissues.

The Ig superfamily of cell adhesion molecules (CAM) is expressed in a wide variety of cell types, including neurons, leukocytes, epithelial, and endothelial cells. Collectively, they function by both homophilic and heterophilic binding. Their heterogeneous expression pattern implicates them in diverse biological processes, such as brain development, immune responses, tissue sorting, morphogenesis, and development of the vascular network. They are characterized by the presence of one or more Ig-like domains in their extracellular region. In addition, the ectodomain of Ig-CAMs may contain various numbers of fibronectin type III (FNIII) repeats, which possess the Arg-Gly-Asp (RGD) cell attachment site. Neural cell adhesion molecules (N-CAMs) and the intercellular cell adhesion molecules (ICAMs) are the best-studied members of this family.

Integrins belong to a superfamily of non-covalently bound heterodimeric membrane receptor glycoproteins. They are composed of a variable α-subunit of 150-170 kDa and a conserved 95-kDa β-subunit. Although both subunits are required for adhesion, the binding specificity primarily depends on the extracellular portion of the α-subunit. While generally classified as adhesion molecules, integrins also play an important role in signal transduction. Signal transduction through integrins occurs in two directions - moving from the extracellular microenvironment into the cell (outside-in signaling) and from the cytoplasm to the extracellular domain of the receptor (inside-out signaling). Among the signaling molecules involved in integrin-mediated cell survival is focal adhesion kinase, which is activated following integrin ligation. It activates downstream survival pathways, such as PI 3-kinase, Akt, and MAPK/ERK. In response to specific stimuli, integrins that are generally diffused over the cell surface cluster in focal contacts. Their combined affinities create a region with sufficient adhesive capacity to adhere to the ECM. This allows cells to bind to a large numbers of matrix molecules simultaneously while still maintaining their ability to explore their environment.

Selectins are expressed primarily on leukocytes and endothelial cells. They play an important role in host defense mechanisms. In contrast to other CAMs, selectins bind to carbohydrate ligands. Hence, the resulting binding forces are relatively weak. This allows selectin-mediated interactions between leukocytes and endothelial cells and promotes rolling of the leukocytes along the endothelium. L-selectins are expressed on most leukocytes, E-selectins are inducible on vascular endothelium upon stimulation with cytokines, and P-selectins are found on activated platelets and vascular endothelium.

Dysregulation of several CAMs, particularly the Ig-CAMs, has been linked to tumor progression and metastasis making them a suitable target for therapeutic intervention. Also, increased expression of CAMs on the vascular endothelium is postulated to play an important role in atherogenesis. CAMs also play critical roles in the recruitment and migration of cells to sites of inflammation. Hence, these molecules have become targets for the development of drugs for treatment of cancer, inflammation, and autoimmune diseases.

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Cell Adhesion Inhibitors

Product	Cat. No.	Comments	Size
H-Arg-Gly-Asp-OH	**03-34-0029**	Amino acid sequence within fibronectin that mediates cell attachment.	25 mg
H-Arg-Gly-Asp-Ser-OH	**03-34-0002**	Shown to inhibit fibronectin function by binding to platelet-binding sites.	25 mg
BAY 11-7082	**196870**	Potential anti-inflammatory agent that decreases nuclear translocation of NF-κB and inhibits TNFα-induced surface expression of the endothelial-leukocyte cell adhesion molecules E-selectin, VCAM-1, and ICAM-1. Selectively and irreversibly inhibits the TNFα-inducible phosphorylation of IκB-α (IC_{50} = 10 μM).	10 mg
BAY 11-7085	**196872**	Exhibits biological properties similar to that of BAY 11-7082 (Cat. No. 196870). BAY 11-7085 has also been shown to have potent anti-inflammatory properties *in vivo*.	10 mg
Cyclo(Arg-Gly-Asp-D-Phe-Val)	**182015**	Potent inhibitor of cell adhesion. Inhibits tumor cell adhesion to laminin and vitronectin substrates.	1 mg
Cyclo[Asp(OBzl)-D-Phe-MeVal-Arg(Mtr)-Gly]	**182020**	A negative control compound for cyclo[RGDf-N(Me)V]. Starting material for the synthesis of cyclo[RGDf-N(Me)V]. The final cyclized peptide product, cyclo[RGDf-N(Me)V], is a potent inhibitor of vitronectin and fibrinogen binding to the $\alpha_V\beta_3$ receptor (IC_{50} = 580 pM).	1 mg
FR-1	**05-23-1701**	A cyclic peptide containing the cell binding domain Arg-Gly-Asp and associated cell migration Pro-Ala-Ser-Ser sequences of fibronectin. A potent inhibitor of ADP-induced platelet aggregation (IC_{50} = 7.6 μM).	1 mg
H-Gly-Arg-Ala-Asp-Ser-Pro-OH	**03-34-0052**	Inactive control peptide for fibronectin inhibitors.	5 mg 25 mg
H-Gly-Arg-Gly-Asp-Ser-OH	**03-34-0027**	A cell-binding protein domain that competitively inhibits direct binding of fibroblasts to fibronectin. Also, reported to inhibit the migration of vascular smooth muscle cells into fibrin gels.	25 mg
H-Gly-Arg-Gly-Asp-Ser-Pro-OH	**03-34-0035**	Shown to inhibit fibronectin binding to platelet-binding sites.	5 mg 25 mg
H-Gly-Arg-Gly-Asp-Thr-Pro-OH	**03-34-0055**	Inhibits binding of fibrinogen, fibronectin, vitronectin, and von Willebrand factor to platelets. Also inhibits cell attachment to collagen, fibronectin, and vitronectin.	5 mg 25 mg
LFA-1 Inhibitor	**435310**	An N-benzoylated tryptophan derivative that acts as an inhibitor of LFA-1 (leukocyte functional antigen-1)-meditated lymphocyte proliferation and adhesion. Binds to LFA-1 and prevents the interaction with its native protein ligand ICAM-1 (IC_{50} = 1.4 μM)	10 mg
Pentoxifylline	**516354**	A non-selective phosphodiesterase inhibitor that inhibits the adhesion of T cells to the β_1 and β_2 integrin ligands VCAM-1 and ICAM-1.	500 mg
Probucol	**529618**	A phenolic antioxidant that inhibits the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), in animal models and HUVEC.	1 g
P-Selectin Antagonist (Galloyl-N-gaba-WVDV-OH)	**561308**	A specific, high affinity inhibitor of human P-selectin ligand (IC_{50} = 15.4 nM). Displays weaker affinity towards mouse P-selectin, human L, and E-selectins. Shown to block monocyte-derived HL-60 cell adhesion to P-selectin-transfected CHO cells (EC_{50} = 74 nM).	5 mg

DNA Methyltransferase Inhibitors

DNA methylation is one of the most prevalent epigenetic modifications of DNA in mammalian genomes. It is achieved by DNA methyltransferases that catalyze the addition of a methyl group from S-adenosyl-L-methionine to the 5-carbon position of cytosine. Methylation at cytosine plays an important role in regulating transcription and chromatin structure. Three families of DNA methyltransferase genes have been identified in mammals. They include *Dnmt1, Dnmt2* and *Dnmt3*. Dnmt1 is constitutively expressed in proliferating cells and its inactivation results in demethylation of genomic DNA and embryonic death. Dnmt2 is expressed at low levels in adult tissues. Its inactivation does not affect DNA methylation or maintenance of methylation. Dnmt3 (Dnmt3a and Dnmt3b) is strongly expressed in embryonic stem cells, but is down-regulated in differentiating embryonic stem cells and in adult somatic cells.

Most mammalian transcription factors bind GC-rich DNA elements. Methylation of these elements abolishes the binding capacity. CpG methylation is shown to induce histone deacetylation, chromatin remodeling and gene silencing through a transcription repressor complex. CpG islands are often located around the promoters of housekeeping genes and are not methylated. On the contrary, the CG sequences in inactive genes are usually methylated to suppress their expression.

Aberrant DNA methylation has been linked to several pathological conditions. Mutations in DNA methyltransferase 3b are known to cause ICF (immunodeficiency, centromere instability and facial anomalies) syndrome. Over-expression of DNA methyltransferases has been implicated in the development of several tumors. About 25% of all mutations in the p53 gene in human cancers are reported to occur at CpG sites. Methylation of these sites can inactivate and silence tumor suppressor genes. Abnormal DNA methylation also occurs during aging and alters gene activity, thus affecting a variety of cellular functions.

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DNA Methyltransferase Inhibitors

Product	Cat. No.	Comments	Size
5-Aza-2′-Deoxycytidine	**189825**	A cytosine analog that acts as a DNA methyltransferase inhibitor. Also enhances apoptosis induced by histone deacetylase inhibitors.	25 mg
NEW Zebularine	**691400**	A chemically stable cytidine analog that displays antitumor properties. An inhibitor of DNA methylation and tumor growth both *in vitro* and *in vivo*. Also acts as transition state analog inhibitor of cytidine deaminase by binding at the active site as covalent hydrates.	10 mg 25 mg

DNA and RNA Polymerase Inhibitors

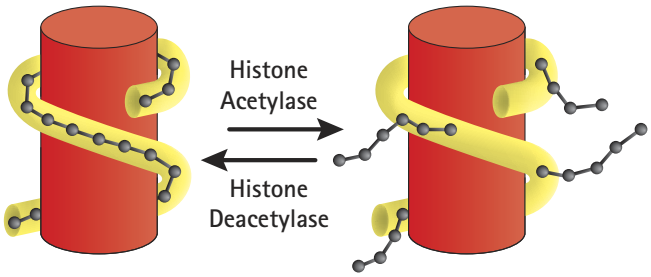
DNA polymerases build DNA by forming a phosphodiester bond between the 5′α-phosphate of one deoxyribonucleotide and the 3′-hydroxyl of another. They cannot initiate DNA synthesis *de novo*, but add deoxynucleotides, one at a time, to the 3′ hydroxyl terminus of a preexisting DNA or RNA strand (a primer). Most DNA polymerases require a template bound to the primer, and extend the primers by synthesizing strands complementary to the template; while most prefer DNA templates, reverse transcriptase prefers RNA templates. Some DNA polymerases, such as terminal transferase, are template-independent. RNA polymerases build (transcribe) RNA strands by forming a phosphodiester bond between the 5′α-phosphate of one ribonucleotide and the 3′-hydroxyl of another. DNA template-dependent RNA polymerases can initiate RNA strand synthesis *de novo*, yielding complementary RNA transcripts. Poly-A polymerase is template-independent, and adds A residues to the 3′-hydroxyl termini of preexisting RNA transcripts. Retroviruses specify RNA polymerases that transcribe RNA using RNA templates.

Inhibitors of DNA and RNA polymerases are invaluable tools in both clinical and research settings. The use of DNA and RNA polymerase inhibitors aids in delineating the mechanistic aspects of transcription and DNA replication, in defining structure-function relationships, and in protein turnover studies. Characterizing mutations that can confer resistance to antibiotics can help identify the genomic loci that encode for the respective subunit of the target enzyme. As DNA and RNA polymerases are among the most attractive drug targets, the knowledge about these inhibitors, their structures, and their modes of action provides the basis for design of new drugs/antibiotics that will be effective against new pathogens and antibiotic-resistant mutants of known pathogens. Because some of these agents block specific steps (transcription) in the processes that lead from DNA to protein, their use can help delineate the role of transcriptional control in regulating the expression of target genes in health and disease. Furthermore, some of these inhibitors can be used in studies requiring the synchronization of the cell cycle; also since some have been reported to induce and/or inhibit apoptosis, these represent valuable tools for apoptosis-related studies.

DNA and RNA Polymerase Inhibitors

Product	Cat. No.	Comments	Size
Actinomycin D, *Streptomyces* sp.	**114666**	Antineoplastic antibiotic that inhibits DNA-primed RNA polymerase by complexing with DNA via deoxyguanosine residues. At higher concentrations, DNA polymerase is inhibited.	5 mg 1 set (20 x 200 µg)
Actinomycin D, 7-Amino-	**129935**	A membrane impermeable fluorescent DNA intercalator. Inhibits RNA polymerase far more specifically than DNA polymerase.	1 mg
α-Amanitin, *Amanita* sp.	**129741**	A potent and specific inhibitor of RNA polymerase II and mRNA synthesis in higher eukaryotes.	1 mg
Methyl α-Amanitin Oleate	**454559**	A semi-synthetic derivative of α-Amanitin, *Amanita* sp. (Cat. No. 129741) that is about 30-fold more cell-permeable than α-Amanitin.	100 µg
Aphidicolin	**178273**	A cell synchronization agent that blocks the cell cycle at the early S-phase. Specific inhibitor of DNA polymerase α and δ in eukaryotic cells and in some viruses of animal origin.	1 mg
Novobiocin, Sodium Salt	**491207**	A DNA gyrase inhibitor that can be used for the production of positively supercoiled plasma DNA. Targets the nucleotide-binding site of gyrase B. Inhibits retrovirus RNA-dependent DNA polymerases.	1 g 10 g
Rifampicin	**557303**	Antibiotic that specifically inhibits DNA-dependent bacterial RNA polymerase by forming an inactive complex with RNA polymerase. Does not affect mammalian RNA polymerase.	1 g 5 g
NEW RNA Polymerase III Inhibitor	**557403**	A cell-permeable broad spectrum inhibitor of RNA polymerase III (IC_{50} = 27 µM and 32 µM for human and *S. cerevisiae* RNA pol. III, respectively).	10 mg

Histone Acetylase and Deacetylase Inhibitors



Gene expression, to a large extent, is controlled by a host of protein complexes that continuously pack and unpack the chromosomal DNA from the inaccessible, tightly packed nucleosomal particles to the accessible, unwound nucleosomal particles. This packing and unpacking is achieved by the acetylation and deacetylation of the histones in the nucleosomal core. Acetylated histone proteins confer accessibility of the DNA template to the transcriptional machinery for expression. Histone acetylation has been linked to gene-specific activation by transcription factors. It plays an important role in cell cycle control and has been linked to uncontrolled cell proliferation. Histone deacetylases (HDAC), on the other hand, are chromatin-remodeling factors that act as transcriptional repressors or silencers of genes. They regulate histone acetylation by catalyzing the removal of acetyl groups on the amino terminal lysine residues of the core nucleosomal histones. Studies have shown that certain oncogenes repress transcription by recruitment of HDACs. This has led to the interest in small molecules that act as inhibitors of HDAC and have potential for the treatment of cancer. They act as potent inducers of growth arrest, differentiation, and apoptotic cell death in a variety of transformed cells in culture and in tumor bearing animals. They are shown to increase the DNA-binding activities of AP1, CREB and NF-κB transcription factors and are also reported to down-regulate telomerase activity via suppression of hTERT mRNA expression. The best-studied inhibitor of HDAC is Trichostatin A, a hydroxamic acid that complexes with zinc and mediates the acetamide cleavage at the catalytic site.

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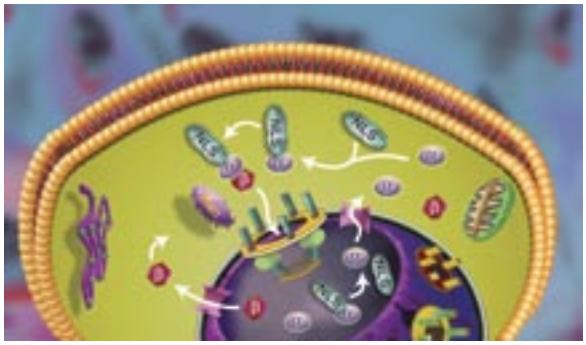
"Grant Application? Oh, just put it over there."

Histone Acetylase and Deacetylase Inhibitors

Product	Cat. No.	Comments	Size
Anacardic Acid	**172050**	A cell-permeable salicylic acid analog that acts as a potent, non-competitive inhibitor of p300 and PCAF (p300/CBP-associated factor) histone acetyltransferase (HAT) activities (IC_{50} ~ 8.5 μM and ~5 μM, respectively).	10 mg
Apicidin, *Fusarium sp.*	**178276**	A potent, cell-permeable inhibitor of histone deacetylase (IC_{50} = 700 pM for parasitic histone deactetylase).	1 mg 5 mg
Histone Deacetylase Inhibitor I	**382147**	A benzamide analog that acts as a histone deacetylase inhibitor (IC_{50} = 2.0 μM) and exhibits anti-tumor properties. Suitable for use in both *in vitro* and *in vivo* applications.	1 mg 5 mg
Histone Deacetylase Inhibitor II	**382148**	A second-generation hybrid polar agent that has been shown to inhibit the activities of histone deacetylase (HDAC) 1 and 3 (ID_{50} = 10 nM and 7 nM, respectively) in MEL DS19/Sc9 cells. The HDAC inhibition is believed to arise as a result of the binding of the hydroxamic moiety to the active site zinc.	5 mg
Histone Deacetylase Inhibitor III	**382149**	An amide analog of Trichostatin A (Cat. No. 647925) that potently inhibits histone deacetylase (IC_{50} = 40 nM for rat liver HDAC and IC_{50} = 100 nM for maize HDAC).	1 mg 5 mg
ITSA1	**419840**	A cell-permeable benzotriazole amide that can be used to counteract Trichostain A-induced cell cycle arrest, histone acetylation, and transcription activation.	25 mg
Oxamflatin	**499700**	An aromatic sulfonamide derivative with a hydroxamic acid group that potently inhibits mammalian histone deacetylase (IC_{50} = 15.7 nM). Acts as a ligand for the enzyme active site metal ion.	1 mg 5 mg
SBHA	**559418**	A histone deacetylase (HDAC) inhibitor with anti-tumor properties. Reported to cause an increase in acetylated histone H4 in MEL cells. Also reported to inhibit human HDAC1 and HDAC3 activities with a similar potency (ID_{50} ~250 - 300 nM). Not available for sale in the USA.	100 mg
Scriptaid	**565730**	A relatively non-toxic hydroxamic acid-containing histone deacetylase (HDAC) inhibitor. Causes over 100-fold increase in histone acetylation in PANC-1 cells at 6 μM.	5 mg
Sirtinol	**566320**	A cell-permeable, specific, and a direct inhibitor of the sirtuin class of histone deacetylase (HDAC) activity. Does not affect human HDAC1. Reported to block Sir2p transcriptional silencing activity *in vivo* (IC_{50} = 25 μM) and NAD-dependent HDAC activity in purified recombinant yeast Sir2p and human SIRT2 *in vitro* (IC_{50} = 68 μM and 38 μM, respectively).	5 mg
Splitomicin	**567750**	A cell-permeable, selective inhibitor of NAD^+-dependent histone deacetylase activity of Sir2 protein (IC_{50} = 60 μM). It creates a conditional phenocopy of a Sir2 deletion mutant in *S. cerevisiae* and sensitizes mammalian cells to a variety of DNA-damaging agents by abrogating Sir2p activity on p53. Acts by either altering or blocking access to the acetylated histone binding pocket.	5 mg
Trichostatin A, *Streptomyces sp.*	**647925**	A potent and reversible inhibitor of histone deacetylase.	1 mg
Valproic Acid, Sodium Salt	**676380**	A cell-permeable, short-chain fatty acid that inhibits histone deacetylase (IC_{50} = 400 μM for HDAC1). Induces differentiation and inhibits proliferation of cell lines derived from human malignant gliomas.	5 g

Nuclear Import/Export Inhibitors



Proteins required for nuclear functions are specifically transported from the cytoplasm into the nucleus. In general, proteins larger than 25 nm in diameter (~30 kDa) can only enter the nucleus in an energy-dependent process, which calls for the participation of a variety of soluble import factors. Trafficking between the nucleus and the cytoplasm occurs via the nuclear pore complexes (NPCs). NPCs are large supramolecular assemblies of ~125-mDa and contain about 100 polypeptides embedded in the double-membrane nuclear envelope. The NPCs allow passive diffusion of ions and small molecules, whereas nuclear proteins, RNAs, and ribonucleoproteins larger than ~9 nm in diameter are selectively and actively transported by a signal-mediated and energy-dependent mechanism. The signal for import is provided by a peptide sequence in the encoded protein known as the nuclear localization signal (NLS). The presence of several different NLSs and import factors suggests the existence of multiple pathways for such an import.

A number of nuclear transport receptors known as importins (karyopherins), transportins, and Ran-binding proteins recognize the NLS and mediate "docking" at the nuclear pore. Importin-α (karyopherin-α), the cytoplasmic receptor for NLS-bearing proteins, binds importin-β via a specific binding domain. Importin-β interacts with the importin-α bound to the NLS and acts as a carrier of the NLS/importin-α/β trimer. This trimeric complex docks to the cytoplasmic filaments of the NPC via importin-β. Subsequent passage of import substrates from the NPC into the nuclear interior requires the small GTPase, Ran, which plays a crucial role in both import/export pathways and determines the directionality of nuclear transport. Once in the nucleus, importin-β binds RanGTP and the import complex is disassembled and the substrate is retained in the nucleus. Ran is reported to shuttle between the nucleus and the cytoplasm and its recycling is essential for nuclear transport. In the cytoplasm, Ran is kept primarily in its GDP-bound form to facilitate import. On the other hand, in the nucleus, Ran is bound to GTP through RCC1, which facilitates export of proteins.

Malfunctioning of the nucleo-cytoplasmic transport is profoundly involved in a number of diseases. Defects in nuclear pore complex components have been implicated in several autoimmune disorders and cancers. At least 11 chromosomal rearrangements in acute leukemia involve nuclear pore protein (nucleoporin) genes. Leukemias associated with nucleoporin gene rearrangements have been reported to be more refractory to therapeutic intervention.

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Nuclear Import/Export Inhibitors

Product	Cat. No.	Comments	Size
Leptomycin A, *Streptomyces sp.*	**431051**	An antifungal antibiotic that acts as an inhibitor of nuclear export. Inhibits nucleo-cytoplasmic translocation of human immunodeficiency virus type 1 regulatory protein (Rev) at nanomolar concentrations.	1 µg
Leptomycin B, *Streptomyces sp.*	**431050**	A potent inhibitor of CRM1-mediated (exportin-1) nuclear export. Shown to inhibit nucleo-cytoplasmic translocation of human immunodeficiency virus type 1 regulatory protein (Rev) at nanomolar concentrations and block Rev-dependent export of mRNA into the cytoplasm. Useful for studies involving nuclear localization and protein trafficking in eukaryotic cells.	1 µg
Ratjadone A, Synthetic	**553590**	A cell-permeable polyketide with antitumor properties. Originally identified as a metabolite from the myxobacterium *Sorangium cellulosum* for its antibiotic activities against yeasts and filamentous fungi, ratjadones inhibit nuclear export of LR-NES (leucine rich-nuclear export signal)-containing proteins by covalently binding to CRM1 (Chromosome region maintenace 1).	2 µg

Poly(ADP-ribose) Polymerase (PARP) and Poly(ADP-ribose) Glycohydrolase (PARG) Inhibitors

Poly(ADP-ribosyl)ation (pADPr) is a covalent post-translational modification process that occurs during DNA repair, replication, and transcription. It is brought about by poly(ADP-ribose)polymerases (PARP), which are activated by breaks in DNA strands. PARPs are a group of Zn^{2+}-binding multi-functional enzymes that catalyze the transfer of ADP-ribose (ADPr) units onto protein acceptors to produce linear and/or branched polymers of ADPr. Upon binding to DNA strand breaks, activated PARP cleaves NAD^+ into nicotinamide and ADP-ribose and polymerizes ADP-ribose onto nuclear acceptor proteins, such as histones and transcription factors.

The 'classical' 113-kDa type I PARP is the major contributor of the poly(ADP-ribosyl)ating activity in higher eukaryotes. Type II PARP is smaller than the classical zinc-finger-containing PARP and is belived to participate in DNA repair during apoptosis. Type III PARP is a large protein containing ankyrin repeats and a PARP catalytic domain.

PARP consists of three domains: a DNA-binding domain (DBD), an automodification domain, and a catalytic domain. The DBD, a 42-kDa N-terminal region, extends from the initiator Met to Thr^{373} in human PARP. It contains two zinc fingers and two helix-turn-helix motifs and is rich in basic residues, which are involved in the interaction of the enzyme with DNA. The automodification domain located in the central region, resides between Ala^{374} and Leu^{525} in human PARP. A BRCT (BRCA1 C-terminus) domain that lies between Ala^{384} and Ser^{479} and consists of about 95 amino acids is found in several proteins that regulate cell-cycle checkpoints and DNA repair. BRCT domains are protein-protein interaction modules that allow BRCT-motif-containing proteins to establish strong and specific associations. The C-terminal catalytic domain, a 55-kDa segment, spans residues Thr^{526} to Trp^{1014} in human PARP. The catalytic activity of this fragment is not stimulated by DNA strand breaks. It corresponds only to the basal activity of the native enzyme. The ADPr transferase activity has been confined to a 40-kDa region at the extreme C-terminus of the enzyme, which is referred to as the minimal catalytic domain. This region can catalyze the initiation, elongation, and branching of ADPr polymers independently of the presence of DNA. The deletion of the last 45 amino acids at the C-terminal end of this domain completely abolishes enzyme activity. Residues spanning positions Leu^{859} to Tyr^{908} in human PARP are well conserved and comprise the 'PARP signature' sequence.

The extent of poly(ADP-ribosyl)ation is an important determinant of NAD^+ levels in cells. In normal, undamaged cells, NAD^+ levels range from 400 to 500 μM. However, PARP activation following DNA damage by radiation or cytotoxic agents reduces NAD^+ levels to about 100 μM within about 15 minutes. It is believed that during its automodification PARP becomes more charged, since each residue of ADPr adds two negative charges on to the molecule. This establishes an electro-repulsive gradient between the polymers of ADPr covalently linked to the enzyme and DNA. When the charge becomes too negative, the reaction reaches a 'point of repulsion' and the interaction between PARP and DNA is lost. The poly(ADP-ribosyl)ated PARP molecule is consequently freed from the DNA strand break and its catalytic activity is abolished. Subsequently, poly(ADP-ribose) glycohydrolase (PARG) hydrolyses the polymers present on PARP, thereby allowing it to resume a new cycle of automodification in response to DNA damage. The presence of PARG during PARP automodification restores both its affinity for DNA and its catalytic activity.

DNA damage, the single most important factor in the regulation of poly(ADP-ribosyl)ation reactions, can stimulate the catalytic activity of PARP by about 500-fold. Inhibition of PARP is shown to reduce DNA repair, increase the cytotoxicity of DNA-damaging agents, and enhance apoptosis. The cytotoxicity of PARP inhibitors is due to an increase in the half-life of DNA strand break, which increases genomic instability. PARP cleavage by caspase-3 is considered as an early event in apoptotic cell death. PARP degradation has also been reported during necrosis, although believed to be through a different process.

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Poly(ADP-ribose) Polymerase (PARP) and Poly(ADP-ribose) Glycohydrolase (PARG) Inhibitors

Product	Cat. No.	Comments	Size
ADP-HPD, Dihydrate, Ammonium Salt	**118415**	An amino analog of ADP-ribose that acts as a highly potent, noncompetitive, and specific inhibitor of PARG (IC_{50} = 120 nM) vs. ADP-ribose (IC_{50} = 120 μM).	60 μg 1 set (5 x 60 μg)
3-Aminobenzamide	**165350**	An inhibitor of PARP that has minimal effect on bacterial toxin-mediated ADP-ribosylation.	100 mg
4-Amino-1,8-naphthalimide	**164585**	A potent inhibitor of poly(ADP-ribose) polymerase (PARP) (IC_{50} = 180 nM) that significantly potentiates the cytotoxicity effects of γ-irradiation.	100 mg
5-Aminoisoquinolinone, Hydrochloride	**164300**	A cell-permeable, water-soluble analog of isoquinoline that acts as a potent and specific inhibitor of PARP (IC_{50} = 240 nM for PARP isolated from calf thymus). Reported to inhibit hydrogen peroxide-induced PARP activity in human cardiac myoblasts (Girardi cells) (IC_{50} ~10 μM).	1 mg 5 mg
DPQ	**300270**	A very potent and selective poly(ADP-ribose)polymerase (PARP) inhibitor (IC_{50} = 40 nM).	1 mg
NEW EB-47	**324473**	A cell-permeable, adenosine-substituted, isoindolinone compound that acts as a potent inhibitor of PARP-1 (IC_{50} = 45 nM).	1 mg
5-Iodo-6-amino-1,2-benzopyrone	**407850**	A lipophilic PARP inhibitor that offers protection against peroxynitrite and hydroxyl radicals *in vitro* and *in vivo*. Abrogates peroxynitrite-induced mitochodrial transmembrane potential ($\Delta\psi_m$) reduction.	5 mg
1,5-Isoquinolinediol	**419800**	A potent inhibitor of poly(ADP-ribose) polymerase (PARP; IC_{50} = 390 nM).	5 mg
NU1025	**493800**	A potent PARP inhibitor (IC_{50} = 400 nM) that potentiates the cytotoxicity of various DNA-active agents, including the DNA-methylating compound MTIC, the DNA strand break-inducing drug temozolomide, topotecan, bleomycin, and ionizing radiation in murine L1210 leukemia cells, Chinese hamster ovary cells, and in a variety of human tumor cell lines.	5 mg
6(5H)-Phenanthridinone	**516700**	An immunomodulator and a potent inhibitor of PARP (IC_{50} = 300 nM).	100 mg
PJ34	**528150**	A potent anti-inflammatory agent and an inhibitor of PARP (EC_{50} = 20 nM). Shown to be about 10,000-fold more potent than the prototypical PARP inhibitor, 3-Aminobenzamide (Cat. No. 165350) (EC_{50} = 200 μM).	1 mg 5 mg
NEW TIQ-A	**612100**	A cell-permeable, potent inhibitor of PARP (IC_{50} = 450 nM for bovine recombinant PARP-1).	1 mg

PARP Inhibitor Set

Provided as a 5 vial set. Each set contains 100 mg of 3-Aminobenzamide (Cat. No. 165350) and 5 mg each of 5-Iodo-6-amino-1,2-benzopyrone (Cat. No. 407850), 1,5-Isoquinolinediol (Cat. No. 419800), and NU 1025 (Cat. No. 493800), and 1 mg of DPQ (Cat. No. 300270).

Cat. No. 528820 **1 set**

Now Available ...

PARP Cellular ELISA Kit	Cat. No. QIA105	1 kit
PARP Cleavage Detection Kit	Cat. No. 512729	1 kit

Telomerase Inhibitors

Telomerase is a specialized ribonucleoprotein composed of a catalytic subunit telomerase reverse transcriptase (TERT), and two other subunits known as telomerase associated protein 1 (TP1), and a ~445-nucleotide long telomerase RNA component (TR). Telomerase stabilizes telomere lengths by adding hexameric (TTAGGG) repeats to the ends of chromosomes, thereby circumventing the cumulative damage that normally occurs during mitotic cell division. Telomerase recognizes the G-rich strand of an existing telomere repeat sequence and elongates it in the 5′-to-3′ direction. Progressive loss of telomeres, a key feature of normal cells, is considered to be a major regulator of cellular senescence. Tumor cells overcome this problem by overexpressing telomerase. As cancer cells divide more often, on an average, they possess shorter telomeres than normal cells. Hence, without an active telomerase to maintain telomere length, cancer cells could reach critically short telomere at a faster pace than normal cells. Telomerase activity, which is practically undetectable in normal cells, is detected in the majority of tumor cells. The presence of telomerase activity is correlated with poor clinical outcome in cancer patients. Hence, telomerase inhibitors are considered as potential therapeutic agents for the management of tumor progression.

Promising approaches for telomerase inhibition include the use of mutant dominant/negative versions of human TERT (hTERT) and the use of antisense oligonucleotides directed against the template RNA component (hTR) of the telomerase holoenzyme. These telomerase inhibitors reduce telomerase activity and lead to progressive shortening of telomeres with each cell division, ultimately causing cells to undergo apoptosis.

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Telomerase Inhibitors

Product	Cat. No.	Comments	Size
3′-Azido-3′-deoxythymidine	**194348**	Inhibitor of HIV-1 reverse transcriptase that blocks the incorporation of nucleotides into newly synthesized DNA. Causes irreversible telomere shortening.	10 mg
AZT, Triphosphate, Tetralithium Salt	**194950**	A reverse transcriptase inhibitor that acts by docking to the active site of HIV-reverse transcriptase. Also reported to inhibit telomerase activity *in vitro* (IC_{50} = 30 μM).	1 μmol
3′–Deoxy-2′,3′-Didehydrothymidine	**257920**	A reverse transcriptase inhibitor with antiviral properties. Has been shown to cause a consistent and rapid telomere shortening in vegetatively growing *Tetrahymena*.	25 mg
Ellipticine, 9-Hydroxy-, Hydrochloride	**324680**	An antitumor alkaloid that acts as a potent inhibitor of topoisomerase II (IC_{50} = 3.3 μM). Also reported to inhibit telomerase activity in cultured pancreatic cancer cells, in a time- and concentration-dependent manner, possibly through inhibition of protein kinases.	10 mg
(-)-Epigallocatechin Gallate	**324880**	A polyphenolic constituent of green tea with potent antitumor, anti-inflammatory, and antioxidant properties. Strongly and directly inhibits telomerase in cell-free systems and in cancer cell lines.	10 mg
PIPER	**528120**	A perylene-based ligand that potently inhibits human telomerase by binding to G-quadruplex DNA. The strongest binding site for PIPER appears to be the 3′-boundary of the G-quadruplex. Can also bind non-specifically to nucleic acids.	10 mg
Telomerase Inhibitor I	**581000**	A non-nucleoside 2,6-diamidoanthraquinone analog that appears to function as a low molecular weight mimic of K^+ in stabilizing the G-quadruplex folded structure, thus inhibiting telomerase activity (IC_{50} = 23 μM for human telomerase).	10 mg
Telomerase Inhibitor III	**581004**	A short hexameric phosphorothioate oligonucleotide (PS-ODN) telomer mimic that inhibits telomerase activity in cell lysates and lengthens cell doubling time *in vitro* and *in vivo* at concentrations less than 2.5 μM.	150 nmol
Telomerase Inhibitor III, Negative Control, Sodium Salt	**581007**	A control containing scrambled sequence of the short hexameric phosphorothioate oligonucleotide PS-ODN (Cat. No. 581004). Useful as a control in experiments to show the specificity of PS-ODN-mediated biological effects.	150 nmol

Telomerase Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Telomerase Inhibitor III, Fluorescein-Labeled, Sodium Salt	**581008**	The short hexameric phosphorothioate oligonucleotide (PS-ODN) TAG-6 (Cat. No. 581004) labeled with the fluorescent tag, 6-FAM [(6-fluorescein-6-carboxamido)hexanoate]. The antisense sequence has been shown to inhibit telomerase activity in cell lysates and lengthen cell doubling time *in vitro* and *in vivo* at concentrations of less than 2.5 μM. Useful for monitoring and confirming cellular uptake.	75 nmol
Telomerase Inhibitor V	**581005**	A non-nucleoside 2,6-diaminoanthraquinone derivative that intercalates DNA and forms a discrete binary complex with G-quadruplex structures, resulting in telomerase inhibition (IC_{50} = 4.5 μM). Does not inhibit *Taq* polymerase even at concentrations of 50 μM.	10 mg
Telomerase Inhibitor VI, Sodium Salt	**581006**	A 13-nucleotide 2′-O-MeRNA possessing terminal phosphorothioate linkages. Potently inhibits telomerase activity (IC_{50} = 2 nM at 23°C and 3 nM at 37°C).	100 nmol
Telomerase Inhibitor VII, Sodium Salt	**581009**	A hexameric phosphorothioate oligonucleotide (PS-ODN) TAG9-2~ (wherein a pair of three-base oligomers are separated by a nine carbon spacer) that inhibits telomerase activity *in vitro* (Minimum inhibitory concentration = 1- 3 μM).	75 nmol
Telomerase Inhibitor VIII	**581010**	A planar, aromatic acridine derivative that acts as potent inhibitor of telomerase *in vitro* (IC_{50} = 2.8 μM in TRAP assay). Believed to act via interaction with four stranded G-quadruplex DNA structures.	10 mg
Telomerase Inhibitor IX	**581011**	A cell-permeable, potent, and reversible inhibitor of telomerase activity (IC_{50} = 670 pM, TRAP lysate prepared from U937 cells). Prolonged treatment with MST-312 has been reported to result in telomere shortening and growth arrest in U937 cells. Does not inhibit the activity of *Taq* DNA polymerase (IC_{50} > 3 μM).	10 mg
TMPyP4	**613560**	A potent inhibitor of human telomerase (IC_{50} = 6.5 μM). TMPyP4 binds strongly to DNA quadruplexes by stacking on the G-tetrads at the core of the quadruplex, resulting in telomerase inhibition. Fluoresces highly in the presence of quadruplex DNA.	25 mg

Telomerase Inhibitor III, TAG-6 Set

A set of 3 vials. Each set contains 150 nmol of Telomerase Inhibitor III (Cat. No. 581004), 150 nmol of Telomerase Inhibitor III, Control (Cat. No. 581007), and 75 nmol of Telomerase Inhibitor III, Fluorescein-Labeled (Cat. No. 581008).

Cat. No. 581020 **1 set**

Telomerase Inhibitor Set I

A set of 4 vials. Each set contains 10 mg of Telomerase Inhibitor V (Cat. No. 581005), 100 nmol of Telomerase Inhibitor VI (Cat. No. 581006), 75 nmol of Telomerase Inhibitor VII (Cat. No. 581009), and 10 mg of 2′,3′-Dideoxyguanosine (Cat. No. 288114).

Cat. No. 581015 **1 set**

Topoisomerase Inhibitors

DNA topoisomerases are nuclear enzymes that regulate the conformational changes in DNA topology by catalyzing the breakage and rejoining of DNA strands during the normal cell cycle. They relieve torsional stress during replication and transcription. Three different types of topoisomerases have been reported in humans; Type I (91-kDa monomer), Type IIα (170-kDa dimer), and Type IIβ (180-kDa dimer). Simpler organisms possess only topoisomerase I; however, higher organisms have all three types of topoisomerases. While topoisomerase IIα is present in all eukaryotes, IIβ is present only in vertebrates and appears to be closely associated with cell differentiation, but not proliferation. Topoisomerases act by catalyzing the breakdown and rejoining reactions in the phosphodiester backbone of DNA. Topoisomerase I reversibly cleaves a single strand in duplex DNA molecule, whereas topoisomerase II breaks and rejoins both DNA strands.

During the past few years topoisomerases have become important chemotherapeutic targets for cancer treatment. Several novel compounds have been developed that can target either topoisomerase I or topoisomerase IIα-/IIβ- isoforms, or all three types of topoisomerases. Inhibition of topoisomerase II is considered to be more challenging due to the complexity of interactions. Most inhibitors of topoisomerase II block the ligation step, leading to stabilized "cleavable complexes" between DNA and the enzyme. Most enzyme inhibitors function by docking into the enzyme active site or nearby allosteric site to block the reaction of the normal substrate. Inhibition of topoisomerase II involves two parts: the aromatic part of the inhibitor molecule intercalates between DNA base pairs and another more polar portion interacts with topoisomerase. Because topoisomerase II inhibitors (e.g., doxorubicin, and etoposide) act as poisons rather than as classical competitive inhibitors, their action is dependent upon the level of the enzyme in cells. Rapidly proliferating cells, which contain relatively higher levels of topoisomerase II, appear to be more sensitive to these agents.

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Topoisomerase Inhibitors

Product	Cat. No.	Comments	Size
Aclacinomycin A, *Streptomyces galilaeus*	**112270**	An anthracycline antitumor agent that inhibits topoisomerase I/II. Also inhibits the degradation of ubiquitinated proteins by blocking the chymotrypsin-like activity of the 20S proteasome (IC_{50} = 52 μM).	50 mg
AG 1387	**658520**	An analog of tyrphostin AG 555 (Cat. No. 658404) that acts as an inhibitor of EGFR tyrosine kinase and of DNA topoisomerase I.	5 mg
Aurintricarboxylic Acid	**189400**	A polyanionic, polyaromatic compound that inhibits apoptotic cell death in various cell types induced by a variety of factors. A potent inhibitor of DNA topoisomerase II.	100 mg
Camptothecin, *Camptotheca acuminata*	**208925**	A reversible DNA topoisomerase I inhibitor that binds to and stabilizes the topoisomerase-DNA covalent complex.	50 mg
Camptothecin, 10-Hydroxy-, *Camptotheca acuminata*	**390238**	A powerful DNA topoisomerase I inhibitor that reduces DNA synthesis in murine hepatoma cells. Has a selective inhibitory effect on the phosphorylation of histones H1 and H3, but is less effective on other histones.	25 mg
Daunorubicin, Hydrochloride	**251800**	Potent anticancer agent that inhibits RNA and DNA synthesis by intercalating into DNA. Inhibits eukaryotic topoisomerase I and II.	5 mg
Doxorubicin, Hydrochloride	**324380**	An anti-tumor antibiotic and a highly effective myotoxin that inhibits topoisomerase II (IC_{50} = 100 nM).	10 mg
Ellipticine	**324688**	A topoisomerase II inhibitor. Acts as an intercalative alkaloid that stimulates topoisomerase II-mediated DNA breakage.	10 mg
Epirubicin Hydrochloride	**324905**	A stereoisomer of doxorubicin that exhibits reduced cardiotoxicity. Its antitumor actions are mediated by targeting topoisomerase II.	5 mg
Etoposide	**341205**	A topoisomerase II inhibitor (IC_{50} = 59.2 μM) that induces apoptosis in mouse thymocytes and in HL-60 human leukemia cells.	25 mg

Topoisomerase Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Etoposide Phosphate	**341206**	A water-soluble derivative of the topoisomerase II inhibitor, etoposide (Cat. No. 341205).	5 mg
Genistein	**345834**	An inhibitor of protein tyrosine kinases (IC_{50} = 2.6 μM for EGFR tyrosine kinase) that also inhibits topoisomerase II activity *in vitro*.	20 mg 50 mg
β-Lapachone	**428022**	A DNA topoisomerase I inhibitor of plant origin; however, unlike Camptothecin (Cat. No. 208925), β-lapachone does not stabilize the cleavable complex, indicating a different mode of action.	5 mg
Merbarone	**445800**	An anticancer drug that inhibits the catalytic activity of DNA topoisomerase II (topo II) without damaging DNA or stabilizing DNA-topo II cleavable complexes (IC_{50} = 20 μM for purified mammalian topoisomerase II versus IC_{50} ~200 μM for topoisomerase I).	25 mg
Netropsin, Dihydrochloride, *Streptomyces netropsis*	**480676**	Unusual N-methylpyrrole containing oligopeptide that binds to AT-rich sequences of double-stranded DNA, especially in the minor grove. Protects these DNA regions from DNase I and other endonucleases. Inhibits topoisomerases.	10 mg
Nogalamycin, *Streptomyces nogalater*	**488200**	An aromatic polyketide antibiotic that inhibits DNA topoisomerase I but has no effect on topoisomerase II. Inhibits the DNA unwinding activity of human DNA helicase II (ID_{50} = 420 nM).	5 mg
Rebeccamycin, *Saccharothrix aerocolonigenes*	**553700**	An indolocarbazole-derived antibiotic that shows significant anti-tumor properties *in vitro* (IC_{50} = 480 nM against murine B16 melanoma cells and IC_{50} = 500 nM against P388 leukemia cells). Weak inhibitor of topoisomerase I.	250 μg
Suramin, Sodium Salt	**574625**	An inhibitor of topoisomerase I and II. Uncouples G-proteins from receptors presumably by blocking their interaction with intracellular receptor domains. A competitive inhibitor of reverse transcriptase.	50 mg 200 mg
Topotecan, Hydrochloride	**614800**	A water-soluble, semi-synthetic derivative of camptothecin (Cat. No. 208925). A potent DNA topoisomerase I inhibitor. Has been shown to exhibit antitumor activity against several forms of cancer.	1 mg

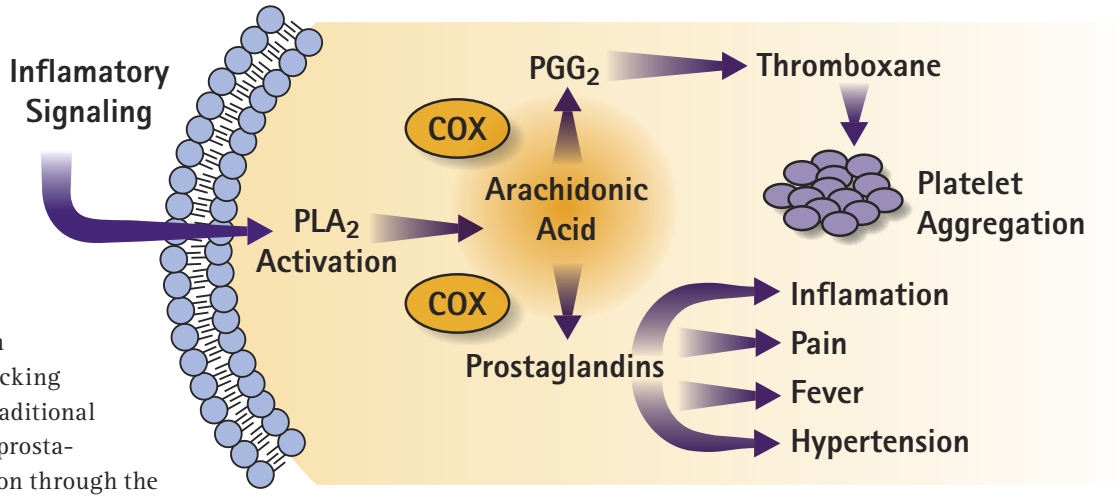
Lipid Signaling

Cyclooxygenase (COX) Inhibitors

Cyclooxygenases (COX) are bifunctional hemoproteins that catalyze both the bisoxygenation of arachidonic acid to form PGG_2 and the peroxidative reduction of PGG_2 to form PGH_2. Hence, COX has two different active sites. On one side, it has the cyclooxygenase active site, and on the opposite side is an entirely separate peroxidase site, which is required to activate the heme groups that participate in the cyclooxygenase reaction. The enzyme complex is a dimer of identical subunits, two cyclooxygenase active sites and two peroxidase active sites. COX-1 is a constitutive enzyme associated with the endoplasmic reticulum. It is responsible for maintaining normal physiologic function and is considered as a "housekeeping" enzyme. COX-2 is an inducible enzyme mainly associated with the nuclear envelope and is primarily associated with inflammation. Cytokines and growth factors increase the expression of COX-2, mainly at inflammatory sites, producing prostaglandins, which mediate inflammation, pain, and fever. Increased expression of COX-2 has been associated with increased incidence of colon and breast cancers.

Non-steroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory and analgesic effects through the inhibition of prostaglandin synthesis by blocking COX activity. Traditional NSAIDs inhibit prostaglandin formation through the inhibition of both COX-1 and COX-2. Inhibition of COX-1 is not necessary for anti-inflammatory and analgesic effects but is thought to account for much of the toxicity of traditional NSAIDs. Based on structural differences in the active sites of these two isozymes, several new drugs have been developed that specifically inhibit only COX-2 activity. COX-2 selective inhibitors have the potential to provide the traditional benefits of NSAID with significantly reduced incidence of endoscopic ulcers. The selective COX-2 inhibitors have great clinical significance because they can allow the preservation of COX-1 activity, which is essential in maintaining prostaglandins that are important for normal platelet function and protection of the gastrointestinal mucosa, and still inhibit COX-2 to reduce inflammation and other pathologic processes.

Due to the consideration of "inflammation as a factor" there has been an upsurge of interest in COX-2 inhibitors as possible candidates for the treatment of Alzheimer's disease. NSAIDs are believed to inhibit human Aβ aggregation *in vitro* and reverse the β-sheet conformation of preformed fibrils. Several epidemiological studies have indeed shown that groups of people taking nonsteroidal anti-inflammatory drugs (NSAIDs), for unrelated conditions, such as rheumatoid arthritis, have a reduced incidence of Alzheimer's disease.



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Cyclooxygenase (COX) Inhibitors

Product Name	Cat. No.	Comments	Size
COX-1 Inhibitor, FR122047	**236005**	A potent, cell-permeable, and selective inhibitor of COX-1 (IC_{50} = 28 nM; human recombinant COX-1). Does not significantly inhibit COX-2 (IC_{50} = 65 μM, human recombinant COX-2).	5 mg
COX-2 Inhibitor I (LM-1685)	**236011**	A potent and selective inhibitor of COX-2 (IC_{50} = 650 nM) from human monocytes. Displays only very weak activity against COX-1 from human platelets (IC_{50} >10 μM) and in whole blood (IC_{50} >100 μM).	5 mg
COX-2 Inhibitor, PTPBS	**236010**	A highly selective and potent inhibitor of COX-2 (IC_{50} = 32 nM for COX-2 vs. 55.1 μM for COX-1). Does not exhibit gastric toxicity in a fasting rat model at doses as high as 200 mg/kg.	5 mg
NEW COX-2 Inhibitor II (SC-791)	**236012**	A cell-permeable isoxazolyl-benzenesulfonamide compound that acts as a potent and highly selective inhibitor of COX-2 both *in vitro* (IC_{50} = 4 nM for hCOX-2 vs. 114 μM for hCOX-1) and *in vivo*.	5 mg
Curcumin, *Curcuma longa* L.	**239802**	An anti-inflammatory, antitumor agent that inhibits COX (IC_{50} = 52 μM) and 5-lipoxygenase (IC_{50} = 8 μM) activities.	100 mg
Diclofenac, 4′-Hydroxy-	**287845**	A metabolite of Diclofenac (Cat. No. 287840). Formed through oxidation of diclofenac by cytochrome P450 2C9. Suppresses prostaglandin E2 (PGE2) formation by specifically blocking COX-2 activity (IC_{50} = 16.9 nM).	100 μg
Diclofenac Sodium	**287840**	Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. A potent inhibitor of COX-1 (IC_{50} = 76 nM) and COX-2 (IC_{50} = 26 nM).	1 g
DuP-697	**317500**	A potent, irreversible, and time-dependent COX-2 inhibitor. Exhibits over 50-fold greater inhibitory potency against human and murine recombinant COX-2 (IC_{50} = 80 nM and 40 nM at 5 and 10 minutes, respectively) than COX-1 (IC_{50} = 9 μM).	5 mg
Ebselen	**324483**	A neuroprotective antioxidant that acts as a non-selective inhibitor of the cyclooxygenases. An excellent scavenger of peroxynitrite. Glutathione peroxidase mimetic.	5 mg
Flufenamic Acid	**343075**	A potent inhibitor of NF-κB-mediated COX-2 expression. Causes mitochondrial uncoupling via a protonophoric mechanism. Potently inhibits human transthyretin (TTR) amyloid fibril formation.	1 g
Flurbiprofen	**344079**	A non-steroidal anti-inflammatory agent that acts as a potent cyclooxygenase inhibitor (IC_{50} = 5 nM for LPS-induced COX in human peripheral blood cells). Reduces Aβ loads and Congo Red staining in APP+PS1 transgenic mice.	100 mg
(±)-Ibuprofen	**401003**	A competitive, and non-selective COX inhibitor (IC_{50} = 4.85 μM for COX-1 and 223 μM for COX-2). Decreases the total Aβ secretion (Aβ40 and 42) in human neuronal cells and offers neuroprotection against glutamate-, nitric oxide-, and superoxide-induced damage.	1 g
(S)-(+)-Ibuprofen	**401004**	A competitive, reversible, and non-selective COX inhibitor (ID_{50} = 8.9 μM for COX-1 and 7.2 μM for COX-2). Reduces the levels of amyloidogenic Aβ42 in WT-APP PS1-M146L CHO cells (50% reduction in Aβ42/Aβ40 quotient at ~200 - 300 μM) and in Tg2576 transgenic mice. Does not affect amyloid precursor protein or Notch processing.	250 mg
Indomethacin	**405268**	A non-steroidal anti-inflammatory, anti-pyretic agent. Non-selective COX inhibitor (IC_{50} = 740 nM for COX-1 and 970 nM for COX-2). Reported to reduce Aβ42 load independently of COX inhibition.	10 g
Indomethacin Amide, N-Octyl-	**405270**	An N-octylamide derivative of Indomethacin (Cat. No. 405268) that acts as a potent and selective COX-2 inhibitor (IC_{50}= 40 nM) compared to COX-1 (IC_{50} = 66 μM).	5 mg
Indomethacin Ester, n-Heptyl-	**405269**	A heptyl ester derivative of Indomethacin (Cat. No. 405268) that acts as a potent and selective COX-2 inhibitor (IC_{50} = 40 nM) compared to COX-1 (IC_{50} > 66 μM).	5 mg
Indomethacin Ester, 4-Methoxyphenyl-	**405271**	A 4-methoxyphenyl ester derivative of Indomethacin (Cat. No. 405268) that acts as a potent and selective COX-2 inhibitor (IC_{50} = 40 nM) compared to COX-1 (IC_{50} > 66 μM).	5 mg

Cyclooxygenase (COX) Inhibitors, *continued*

Product Name	Cat. No.	Comments	Size
Kaempferol	**420345**	A phytoestrogen that offers protection against Aβ25 - 35-induced cell death in neonatal cortical neurons. Blocks Aβ-induced activation of caspase-2, -3, -8, and -9. Acts as an inhibitor of COX-1 (IC_{50} = 180 μM) and COX-2 (IC_{50} ~15 μM).	25 mg
Meloxicam	**444800**	Preferentially inhibits COX-2 (IC_{50} = 4.7 μM) relative to COX-1 (IC_{50} = 36.6 μM).	100 mg
Niflumic Acid	**481987**	A selective inhibitor of COX-2 (K_i = 20 nM for sheep placental COX-2).	1 g
NS-398	**349254**	Selective inhibitor of COX-2 (IC_{50} = 3.8 μM for sheep placental COX-2). Reduces neuronal damage following a stroke.	5 mg
Resveratrol	**554325**	A phenolic product with antifungal, antitumor, and antioxidative properties. A specific inhibitor of COX-1 (ED_{50} = 15 μM). Also inhibits the hydroxyperoxidase activity of COX-1 (ED_{50} = 3.7 μM).	25 mg
SC-236	**565605**	A highly selective and potent inhibitor of COX-2 (IC_{50} = 10 nM for COX-2 vs. IC_{50} = 17.8 μM for COX-1). Exhibits longer half-life and reduced gastric toxicity in fasting rat model.	5 mg
SC-558	**565608**	A potent and selective inhibitor of cyclooxygenase-2 (COX-2; IC_{50} = 9.3 nM). Exhibits 1,900-fold selectivity over COX-1 (IC_{50} = 17.7 μM).	1 mg
SC-560	**565610**	A highly potent and selective inhibitor of COX-1 (IC_{50} = 9 nM). Inhibits COX-2 only at higher concentrations (IC_{50} = 6.3 μM).	5 mg
SC-58125	**565620**	A potent and selective inhibitor of COX-2 (IC_{50} = 50 nM). Weakly but rapidly inhibits COX-1 (IC_{50} >10 μM) in a competitive and reversible manner. Also exhibits a similar profile for human recombinant COX enzymes.	5 mg
SKF-86002	**567305**	A cytokine-suppressive anti-inflammatory drug (CSAID) that also acts as an inhibitor of both cyclooxygenase and 5-lipoxygenase.	5 mg
Sulindac	**574100**	A prodrug that is metabolized to a pharmacologically active sulfide derivative that potently inhibits cyclooxygenase activity. Inhibits chemical carcinogenesis in rodent models and causes regression of adenomas by an apoptotic mechanism.	1 g
Sulindac Sulfide	**574102**	A selective inhibitor of COX-1 (ID_{50} = 500 nM) versus COX-2 (ID_{50} = 14 μM). Reduces Aβ42 load independently of COX inhibition.	5 mg
Sulindac Sulfone	**574105**	A sulfone metabolite of Sulindac (Cat. No. 574100) that has anti-cancer properties but lacks COX inhibitory activity. Also inhibits cell growth and induces apoptosis.	5 mg

Cyclooxygenase Inhibitor Set

Provided as a 4 vial set. Each set contains 100 mg of Meloxicam (Cat. No. 444800), and 5 mg each of NS-398 (Cat. No. 349254), SC-560 (Cat. No. 565610), and Sulindac Sulfide (Cat. No. 574102).

Cat. No. 239783 1 set

3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) Reductase Inhibitors

Regulation of the expression of hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is critical in maintaining normal cholesterol levels in serum and tissues. HMG-CoA reductase inhibitors (statins) are competitive inhibitors of this enzyme and have hypo-cholesterolemic properties. These inhibitors have close resemblance to HMG-CoA. During cholesterol biosynthesis they competitively inhibit the conversion of HMG-CoA to mevalonate, thereby reducing cholesterol biosynthesis in hepatic cells. This results in the enhanced synthesis of LDL-C receptors and increased uptake of LDL-C particles, which enhances cholesterol clearance from the plasma. Ultimately, LDL-C and total cholesterol concentrations are reduced.

HMG-CoA reductase inhibitors differ in their pharmacokinetic properties and drug interaction profiles. For example, Lovastatin and Simvastatin are extensively metabolized by CYP3A4, an isozyme of the P450 system, and thus have the potential to interact with other drugs competing for or inhibiting this isoform. Both Lovastatin and Simvastatin are prodrugs in the lactone form and must be converted to active metabolites by the liver. On the other hand, pravastatin is not extensively metabolized by the P450 system. It is administered in its active hydroxyl acid form and is more hydrophilic and less protein-bound.

3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) Reductase Inhibitors

Product Name	Cat. No.	Comments	Size
Cerulenin, *Cephalosporium caerulens*	**219557**	An antifungal antibiotic that inhibits sterol and fatty acid biosynthesis. In fatty acid synthesis, reported to bind in equimolar ratio to β-keto-acyl-ACP synthase. In sterol synthesis, inhibits HMG-CoA synthetase activity.	5 mg
Fluvastatin	**344095**	A synthetic HMG-CoA reductase inhibitor (IC_{50} = 40 - 100 nM for human liver microsomes) that acts as anti-hypercholesterolemic agent.	25 mg
Lovastatin	**438185**	An anti-hypercholesterolemic agent that inhibits the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.	25 mg
Lovastatin Sodium	**438186**	Carboxylate form of Lovastatin (Cat. No. 438185) that is active in whole cells and cell-free assays.	5 mg
Mevastatin	**474700**	An antibiotic that acts as a potent inhibitor of HMG-CoA reductase, thus suppressing Ras farnesylation.	50 mg
Mevastatin, Sodium Salt	**474705**	Carboxylate form of Mevastatin (Cat. No. 474700) that is active in whole cells and in cell-free assays.	5 mg
Pravastatin, Sodium Salt	**524403**	A water-soluble, competitive inhibitor of HMG-CoA reductase that potently blocks *in vivo* cholesterol synthesis (K_i ~1 nM).	25 mg
Simvastatin	**567020**	A lipophilic HMG-CoA reductase inhibitor that blocks Ras function through inhibition of farnesylation.	50 mg
Simvastatin, Sodium Salt	**567021**	Carboxylate form of Simvastatin (Cat. No. 567020) that is active in whole cells and in cell-free preparations.	5 mg

Lipoxygenase (LOX) Inhibitors

Based on their regiospecificity during interaction with substrates, lipoxygenases (LOX) have been classified as 5-, 8-, 12-, and 15-LOX. They insert oxygen at carbon 5, 8, 12 or 15 of arachidonic acid, forming 5S-, 8S-, 12S-, or 15S-hydroperoxyeicosatetraenoic acid (5-, 8-, 12-, or 15-HPETE). HPETEs can be further reduced by glutathione peroxidase to the hydroxy forms (5-, 8-, 12-, 15-HETE), respectively. 5-LOX is a dioxygenase that catalyzes the incorporation of molecular oxygen into arachidonic acid (oxygenase activity), producing HPETE and then forms the unstable epoxide LTA4 (LTA4 synthase activity). This is followed by the insertion of molecular oxygen at position C5, converting LTA4 to either 5(S)-hydroxy-6-trans-8, 11,14-cis-eicosatetranoic acid (5-HETE) or leukotrienes. Hydrolytic attack of LTA4 by leukotriene A4 hydrolase yields LTB4, a potent neutrophil chemoattractant and stimulator of leukocyte adhesion to endothelial cells. LTA4 can be conjugated with glutathione to form LTC4 by the action of LTC4 synthase. 5-LOX pathway has been implicated in the development and progression of human cancers. Hence, 5-LOX inhibitors have been sought for their chemopreventive effects. Inhibition of 5-LOX activity is shown to block prostate cancer cell proliferation.

12-LOX exists in three distinct forms: the leukocyte-type, the platelet-type, and the epidermal form. The platelet-type 12-LOX converts arachidonic acid to 12-(S)-HETE. The leukocyte type 12-LOX metabolizes arachidonic acid or linoleic acid to either 12(S)-HETE or 15(S)-HETE. The epidermal form of 12-LOX converts arachidonic acid to 12-HETE and 15-HETE. 12-LOX has been shown to be involved in both cancer cell proliferation and survival. Inhibition of 12-LOX blocks cell proliferation and induces apoptosis in carcinosarcoma cells. 8-LOX is expressed in the skin after irritation or treatment with tumor promoters. Compared with other LOX enzymes, 8-LOX has received little attention for its role in carcinogenesis and cancer growth. 15-LOX exists as two isozymes, 15-LOX-1 and 15-LOX-2. It converts arachidonic acid to 15-HPETE which is then reduced by glutathione peroxidase to 15-HETE. The preferred substrate for 15-LOX-1 and 15-LOX-2 are linoleic acid and arachidonic acid, respectively. The 15-LOX-1 product, 13-S-HODE, is reported to enhance cell proliferation and potentiate the mitogenic response to EGF in different cell types.

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Lipoxygenase (LOX) Inhibitors

Product	Cat. No.	Comments	Size
Baicalein	**196322**	Flavone that inhibits the activity of 12-LOX (IC_{50} = 120 nM) and reverse transcriptase. Reduces leukotriene biosynthesis and the release of lysosomal enzymes.	10 mg
Caffeic Acid	**205546**	A selective, non-competitive inhibitor of 5-LOX (ID_{50} = 3.7 μM).	500 mg
Curcumin, *Curcuma longa* L.	**239802**	Inhibitor of 5-LOX (IC_{50} = 8 μM) and COX (IC_{50} = 52 μM). Exhibits anti-tumor and anti-inflammatory properties.	100 mg
Eicosapentaenoic Acid	**324875**	A fatty acid isolated from microscopic algae that acts as an anti-hyperlipoproteinenic agent. Inhibits 5-LOX and reduces thromboxane A2 production.	25 mg
ETYA	**434741**	An inhibitor of Inhibits COX (ID_{50} = 8 μM), 5-LOX (ID_{50} = 10 μM), 12-LOX (ID_{50} = 300 nM), and 15-LOX (ID_{50} = 200 nM) in whole cells.	20 mg
Hinokitiol	**377230**	A cell-permeable metal ion chelator that also acts as a reversible inhibitor of 12-LOX in platelets (IC_{50} = 100 nM).	50 mg
Ketoconazole	**420600**	An anti-fungal agent that acts as an inhibitor of 5-LOX and thromboxane synthase.	50 mg
MK-886	**475889**	A cell-permeable, potent and specific inhibitor of leukotriene biosynthesis (IC_{50} = 102 nM). Prevents the activation of 5-LOX by binding to 5-LOX-activating protein (FLAP); however, it does not affect 5-LOX activity in cell-free systems.	5 mg
NDGA, *Larrea divaricata*	**479975**	An antioxidant and a selective LOX inhibitor (IC_{50} = 200 nM, 30 μM, and 30 μM for 5-LOX, 12-LOX, and 15-LOX, respectively) over COX (IC_{50} = 100 μM).	250 mg
SKF-86002	**567305**	A cytokine-suppressive anti-inflammatory drug that also acts as an inhibitor of both COX and 5-LOX.	5 mg

Phospholipase Inhibitors

Several signal transduction processes in cells utilize lipid derived second messengers. These molecules are generated by the action of phospholipases on cellular lipids. Phospholipase A_2 (PLA_2) hydrolyzes the acyl group from the *sn*-2 position of glycerophospholipids. Two major types of PLA_2 are found in cells - the cytosolic form ($cPLA_2$) and the secretory form ($sPLA_2$). $cPLA_2$, an 85-kDa enzyme, preferentially hydrolyzes phospholipids containing arachidonate at the *sn*-2 position and provides free arachidonic acid for the synthesis of eicosanoids. $cPLA_2$ is found in a variety of cells where it acts as a receptor-regulated enzyme that can mediate agonist-induced arachidonic acid release. It is activated by low levels of Ca^{2+}. $sPLA_2$, following its release from cells, plays an important role in inflammation and in antimicrobial defense. However, excessive activity of $sPLA_2$ has been shown to result in tissue damage and is linked to organ failure associated with critical illness. PLA_2 inhibitors are considered as desirable candidates for control and management of diseases related to eicosanoid production, such as allergy, inflammation, thrombosis, airway secretion and cell proliferation.

Phospholipase C (PLC) is another important member of the family that controls the production of inositol-1,4,5-trisphosphate (IP3). IP3 is involved in cytosolic Ca^{2+} release and diacylglycerol (DAG) production, both of which activate protein kinase C. Phospholipase D (PLD) catalyzes the hydrolysis of phosphatidylcholine to form phosphatidic acid (PA) and released choline headgroup. The PA can itself act as a signal molecule by activating a PA-activated kinase, or can be hydrolyzed to form DAG by the action of PA phosphohydrolase.

Phospholipase Inhibitors

Product	Cat. No.	Comments	Size
$AACOCF_3$	**100109**	A cell-permeable trifluoromethyl ketone analog of arachidonic acid. Potent and selective slow-binding inhibitor of human cytosolic (85 kDa) PLA_2. Causes a significant reduction in thromboxane B_2 production in thrombin-stimulated platelets.	10 mg
ACA	**104550**	Inhibits epinephrine-stimulated thromboxane production (86% at 3.5 μM) via inhibition of PLA_2 in human platelets. Possesses moderate leukotriene antagonist activity.	25 mg
Aristolochic Acid	**182300**	A 1:1 mixture of aristolochic acids I and II. Inhibits PLA_2 from various snake venoms as well as human platelet and synovial fluid PLA_2. Also inhibits ionophore-stimulated PLA_2 activity (IC_{50} = 40 μM) and Ca^{2+}-dependent arachidonic acid released in human neutrophils. Exhibits greater inhibitory activity towards group II PLA_2 versus group I PLA_2.	50 mg
Cepharanthine, *Stephania cepharantha* Hayata	**219500**	A biscoclaurine alkaloid with anti-inflammatory, anti-allergic, and immunomodulatory properties. Inhibits both the α- and the β-form of phospholipase B.	1 g
D609, Potassium Salt	**251400**	Selective inhibitor of phosphatidylcholine-specific phospholipase C (*Bacillus cereus*, K_i = 5-10 μM). Does not inhibit (up to 50 mM) phosphatidylinositol-specific phospholipase C, PLA_2, and PLD. Also inhibits the activity of sphingomyelinase.	5 mg
NEW D609 Prodrug	**251401**	A cell-permeable prodrug form of D609 (Cat. No. 251400) that displays reduced cytotoxicity towards normal cells, but enhanced potency in inducing apoptosis in tumor cells (LD_{50} = 56.6 μM for U937 cells).	5 mg
ET-18-OCH_3	**341207**	A selective inhibitor of phosphatidylinositol-specific PLC (IC_{50} = 15 μM) but does not inhibit phosphatidylcholine-specific PLC or PLD.	5 mg
Methyl Arachidonyl Fluorophosphonate	**454565**	A selective, active site-directed, irreversible inhibitor of both calcium-dependent and calcium-independent cytosolic (85 kDa) PLA_2, but not secretory PLA_2.	1 mg
MJ33	**475865**	A novel active-site directed, specific, competitive, and reversible inhibitor of PLA_2. Shows high specificity for type I (pancreatic) and bee venom PLA_2, but has relatively poor affinity for the type II human synovial PLA_2. MJ33 has shown inhibitory activity against a low pH calcium-independent enzyme, as well as against the PLA_2 activity, which is responsible for permeability barrier homeostasis or esophagitis.	5 mg

Phospholipase Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Neomycin Sulfate	**4801**	An inhibitor of inositol phospholipid turnover. A non-specific PLC inhibitor. Also inhibits phophatidylcholine-PLD activity (IC_{50} = 65 μM).	25 g
Neomycin Sulfate, γ-Irradiated, Tissue Culture Grade	**480100**	An inhibitor of inositol phospholipid turnover. A non-specific PLC inhibitor. Also inhibits phophatidylcholine-PLD activity (IC_{50} = 65 μM).	20 ml
OBAA	**494110**	Potent inhibitor of snake venom PLA_2 (IC_{50} = 70 nM).	10 mg
$PACOCF_3$	**506274**	A novel Ca^{2+}-independent PLA_2 inhibitor (IC_{50} = 3.8 μM). May also inhibit Ca^{2+}-dependent PLA_2 at higher concentrations (IC_{50} = 45 μM).	5 mg
cPLA2α Inhibitor	**525143**	A cell-permeable, highly specific, potent inhibitor of cytosolic PLA2α (IC_{50} = 1.8 nM). Exhibits ~230-fold greater potency in enzyme assays and ~3900-fold greater potency in cellular assays compared to $AACOCF_3$ (Cat. No. 100109).	500 μg
$sPLA_2$-IIA Inhibitor I	**525145**	A highly hydrophobic cyclic pentapeptide that selectively binds and acts as a potent inhibitor of human type IIA secreted PLA_2 (IC_{50} = 12.8 μM). Reported to effectively block $sPLA_2$-IIA-induced PGE_2 production at 100 nM in human rheumatoid synoviocytes and is non-toxic at doses up to 10 μM. Does not affect the activities of porcine $sPLA_2$-IB, *Naja naja* $sPLA_2$-IB, or *Crotalus durissus* $sPLA_2$-IIA even at 10 μM.	1 mg
Quinacrine, Dihydrochloride	**551850**	Phospholipase A_2 (PLA_2) inhibitor. Acts as an acetylcholine antagonist. Also inhibits monoamide oxidase.	100 mg
12-*epi*-Scalaradial, *Cacospongia* sp.	**565650**	Potent inhibitor of bee venom PLA_2 (IC_{50} = 70 nM). Inhibits Ca^{2+} mobilization induced by LTB4 and platelet activating factor.	1 mg
Spermine, Tetrahydrochloride	**5677**	Polyamine that plays an important role in the regulation of cellular proliferation and differentiation. Acts as an inhibitor of PLC-α and an activator of PLC-δ.	5 g
D-*erythro*-Sphingosine, Dihydro-	**300230**	Biosynthetic precursor of sphingosine that inhibits PKC (Chinese hamster ovary cells: IC_{50} = 2.9 μM). Also directly inhibits PLA_2 and PLD.	10 mg
ST638	**567790**	A protein tyrosine kinase inhibitor (IC_{50} = 370 nM) that also inhibits PLD activity in human neutrophils.	5 mg
U-73122	**662035**	Inhibits agonist-induced PLC activation (IC_{50} = 1.0-2.1 μM) in human platelets and neutrophils.	5 mg
U-73343	**662041**	Analog of U-73122 (Cat. No. 662035) that acts as a very weak inhibitor of PLC. Suitable as a negative control.	5 mg

Sphingomyelinase Inhibitors

Ceramide, a sphingosine-based lipid-signaling molecule, has gained serious attention as an important signaling molecule in cell cycle, cell differentiation, apoptosis, and immune response. Ceramide is generated either through *de novo* synthesis mediated by ceramide synthase or through hydrolysis of membrane sphingomyelin by an acid or neutral sphingomyelinase. Acid and neutral sphingomelinases differ in their ion dependence, pH optima, and cellular localization. Recent evidence suggests that the activation of a non-specific lipid scramblase during apoptosis induces the flipping of sphingomyelin from the cell surface to the cytoplasm side of the plasma membrane where it is cleaved by neutral sphingomyelinase to generate ceramide. The production of ceramide induces blebbing of the plasma membrane and aids in rapid engulfment by phagocytes. Neutral sphingomyelinase-released ceramide has also been shown to be essential for capping of L-selectin in lymphocytes.

Some evidence exists indicating that acid sphingomyelinase deficient cells have defects in apoptotic signaling pathways. Sphingomyelin is usually rapidly broken down in the late endosomes and lysosomes. Hence, in acid sphingomyelinase deficiency, sphingomyelin may be kinetically trapped in lysosomes and disrupt endocytic trafficking of raft-associated cell surface signaling molecules. Defects in acid sphingomyelinase have also been linked to lysosomal storage disease known as Niemann-Pick disease.

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Sphingomyelinase Inhibitors

Product	Cat. No.	Comments	Size
Chlorpromazine, Hydrochloride	**215921**	An inhibitor of calmodulin-dependent phosphodiesterase (IC_{50} = 17 μM) that acts as an inhibitor of lysosomal sphingomyelinase.	500 mg
3,4-Dichloroisocoumarin	**287815**	A serine protease inhibitor that blocks daunorubicin-induced neutral sphingomyelinase activation and sphingomyelin hydrolysis.	10 mg
Gentamycin Sulfate	**345814**	Broad-spectrum antibiotic that reduces sphingomyelinase activity in fibroblasts.	1 g
Manumycin A, *Streptomyces parvulus*	**444170**	A potent and selective inhibitor of farnesyltransferase (FTase, IC_{50} = 5 μM) that acts as an irreversible inhibitor of neutral sphingomyelinase.	1 mg
N-SMase Inhibitor, GW4869	**567715**	A cell-permeable, symmetrical dihydroimidazolo-amide that acts as a potent, specific, and non-competitive inhibitor of neutral sphingomyelinase (N-SMase) (IC_{50} = 1 μM, rat brain N-SMase).	1 mg
N^{α}-Tosyl-Phe Chloromethyl Ketone	**616387**	A serine protease inhibitor that blocks daunorubicin-induced neutral sphingomyelinase activation and sphingomyelin hydrolysis.	250 mg 1 g

Neurobiology/Neurodegeneration

Amyloidogenesis Inhibitors

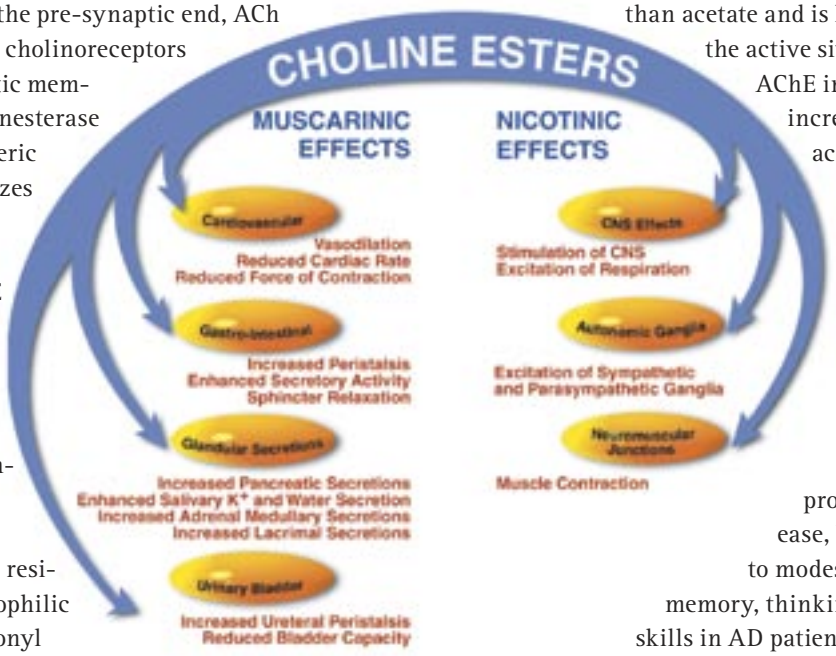
Aβ (β-amyloid) peptide is a major component of neuritic plaques and cerebrovascular amyloid deposits in the brains of patients with Alzheimer's disease (AD). The cellular origin of amyloid precursor protein (APP) that gives rise to Aβ is now well understood. Morphological evidence suggests that APP-immunoreactive neurites, often capped by Aβ deposits, are one of the major sources of parenchymal amyloid. However, other cells, including astroglia, microglia, and vascular cells, may contribute to the formation of Aβ. A long-standing hypothesis has been that Aβ deposits are neurotoxic and are causative factors in the development and progression of AD. Hence, the development of inhibitors of Aβ fibrillogenesis has become an important area of research.

Amyloidogenesis Inhibitors

Product	Cat. No.	Comments	Size
$A\beta_{40}$ Fibrillogenesis Inhibitor (Ac-K(Me)LV(Me)FF-N_H2)	**171581**	Cell-permeable pentapeptide based on the core domain of Aβ, which contains N-methyl amino acids in alternate positions. Displays stability towards denaturation and is resistant to chymotrypsin.	1 mg 5 mg
$A\beta_{42}$ Fibrillogenesis Inhibitor I (LPFFD)	**171586**	Design is based on the central hydrophobic region in the N-terminal domain of Aβ. Binds to the monomeric/dimeric Aβ peptides with high affinity (K_d ~70 nM).	5 mg
$A\beta_{42}$ Fibrillogenesis Inhibitor II (RVVIA-N_H2)	**171587**	Contains the C-terminal sequence of $A\beta_{42}$ with Gly^{38} to Arg substitution, which results in improved solubility and potency.	5 mg
$A\beta_{42}$ Fibrillogenesis Inhibitor III (Ac-LPFFD-N_H2)	**171588**	A modified analog of $A\beta_{42}$ Fibrillogenesis Inhibitor I (Cat. No. 171586). Can cross the blood brain barrier. Exhibits greater stability against proteolytic degradation.	5 mg
$A\beta_{42}$ Fibrillogenesis Inhibitor IV (Ac-LP-(NMe)FFD-N_H2)	**171589**	A modified analog of the end protected $A\beta_{42}$ Fibrillogenesis Inhibitor III (Cat. No. 171588) that acts as a β-sheet breaker. Has increased *in vivo* metabolic stability ($t_{½}$ >24 hours in human plasma and in rat brain homogenate).	5 mg
β-Amyloid Ligand	**171585**	Contains the short Aβ fragment (KLVFF; $A\beta^{16-20}$) and binds stereospecifically to the homologous sequence in full-length Aβ by forming an atypical anti-parallel β-sheet, thus preventing its assembly into amyloid fibrils.	1 mg
Clioquinol	**233165**	A metal ion chelator that crosses the blood-brain barrier and acts as a neurotoxic antibiotic. Reported to dissolve senile plaques and reduce amyloid's ability to clump together, apparently by trapping Cu^{2+} and Zn^{2+} that reduces the build-up of these deposits.	1 g
Flufenamic Acid	**343075**	A non-steroidal anti-inflammatory agent that is reported to inhibit the formation of transthyretin amyloid fibrils.	1 g

Cholinesterase Inhibitors

A large number of autonomic neurons are cholinergic in nature. Cholinergic terminals contain a large number of small acetylcholine (ACh)-containing, membrane-bound vesicles concentrated near the synaptic end. Following their release from the pre-synaptic end, ACh molecules activate cholinoreceptors on the post-synaptic membrane. Acetylcholinesterase (AChE) is a tetrameric protein that catalyzes the hydrolysis of acetylcholine. The active site of AChE includes a serine hydroxyl group that is rendered more nucleophilic through the proton-acceptor action of a nearby histidine residue. The serine residue exerts a nucleophilic attack on the carbonyl carbon of acetylcholine. AChE inhibitors may act by either competitively blocking hydrolysis without reacting with the enzyme, or may acylate the serine hydroxyl group, forming a carbamyl ester, which is more stable than acetate and is less likely to abandon the active site of the enzyme.



AChE inhibitors, which increase the availability of acetylcholine in central synapses, as well as muscarinic agonists, have become the main approach to symptomatic treatment of patients with Alzheimer's disease. These agents do not reverse the progression of the disease, but they do contribute to modest improvements in memory, thinking and reasoning skills in AD patients.

Cholinesterase Inhibitors

Product	Cat. No.	Comments	Size
Diisopropylfluorophosphate	**30967**	Serine protease inhibitor that acts as an irreversible inactivator of AChE.	1 g
Galanthamine, Hydrobromide	**345670**	A cholinesterase inhibitor and antimyasthenic agent that can partially reverse the effects of scopolamine-induced amnesia in rats.	20 mg
(±)-Huperzine A	**385885**	A synthetic, optically inactive, enantiomeric mixture that inhibits AChE activity and acts as a cholinomimetic.	1 mg
(-)-Huperzine A, *Huperzia serrata*	**385886**	Potently inhibits AChE (K_i = 8 nM) in a mixed linear competitive manner. A more potent enantiomer with three-fold activity compared to the racemic mixture, (±)-Huperzine (Cat. No. 385885).	250 µg

Monoamine Oxidase (MAO) Inhibitors

Monoamine oxidase (MAO), a flavin-containing enzyme, catalyzes the oxidative deamination of several naturally occurring monoamines. It regulates the metabolic degradation of catecholamines and serotonin in neural and other target tissues. Two distinct subtypes of MAO have been identified, MAO-A and MAO-B. MAO-A is found in norepinephrine and serotonin nerve terminals in the brain, in human placenta, intestine, and peripheral norepinephrine-secreting nerve terminals. MAO-B is usually found in dopamine-secreting neurons in the brain.

Intestinal MAO-A is believed to protect cells from any exogenous amines contained in foods that might otherwise displace norepinephrine from storage vesicles in adrenergic neurons.

MAO inhibitors prolong the effect of monoamine transmitters. These inhibitors tend to increase the levels of serotonin, dopamine, and norepinephrine in the brain. They have been used as therapeutic agents in the treatment of depression and anxiety. Since they enhance the dopaminergic tone in the brain, they are also used in the treatment of Parkinson's disease.

Monoamine Oxidase Inhibitors

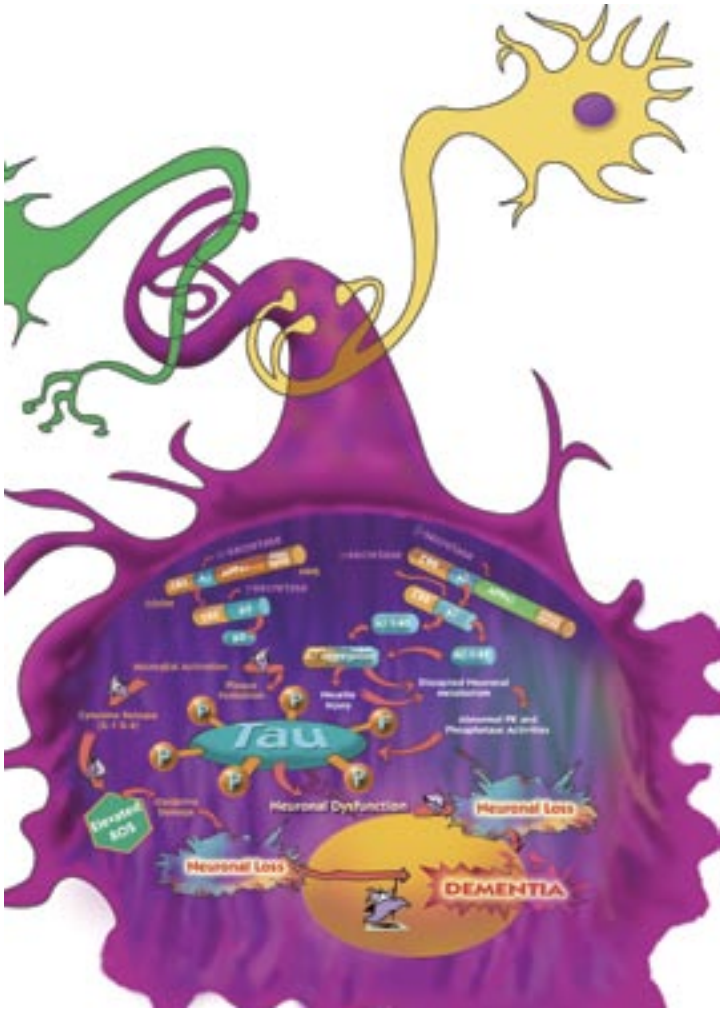
Product	Cat. No.	Comments	Size
R-(–)-Deprenyl, Hydrochloride	**262000**	A selective monoamine oxidase-B (MAO-B)(IC_{50}=17 nM) inhibitor with neuroprotective and vasodilatory properties. Has only a trivial effect on MAO-A enzyme (IC_{50} >100 µM).	100 mg
Quinacrine, Dihydrochloride	**551850**	A phospholipase A_2 inhibitor that also inhibits the activity of monoamine oxidase.	100 mg

Secretase Inhibitors

Deposition of Aβ is an early event in the pathogenesis of Alzheimer's disease (AD). The β-amyloid gene, located on chromosome 21, encodes a transmembrane amyloid precursor protein (APP), which gives rise to Aβ. In normal healthy individuals, Aβ peptides are present only in small quantities as soluble monomers that circulate in the cerebrospinal fluid and blood. However, in AD patients, their levels are significantly increased and they begin to accumulate as insoluble, fibrillar plaques.

Processing of APP *in vivo* occurs by two major pathways. Cleavage of APP at the N-terminus of the Aβ region by β-secretase and at the C-terminus by γ-secretases represents the amyloidogenic pathway for processing of APP. β-secretase cleaves APP between residues Met^{671} and Asp^{672} and yields Aβ peptide plus the C99 fragment. Following β-secretase cleavage, a second cleavage occurs at the C-terminus of Aβ peptide that releases Aβ from C99. This cleavage occurs in the vicinity of residue 712 of the C-terminus. γ-secretase can cleave the C-terminal region at either Val^{711} or Ile^{713} to produce a shorter Aβ peptide ($Aβ_{1-40}$) or the longer Aβ peptide ($Aβ_{1-42}$). The predominant form of Aβ found in the cerebrospinal fluid is the shorter $Aβ_{40}$ peptide. Despite its lower rate of synthesis, $Aβ_{42}$ is the peptide that is initially deposited within the extracellular plaques of AD patients. In addition, $Aβ_{42}$ is shown to aggregate at a much lower concentration than the $Aβ_{40}$ form.

APP can also be processed by α-secretase (TACE), which cleaves within the Aβ domain between Lys^{687} and Leu^{688} and produces a large soluble α-APP domain and the C-terminal fragment containing P3 and C83. The latter can then be cleaved by γ-secretase at residue 711 or 713 to release the P3 fragment. This pathway does not yield Aβ peptide. Hence, shunting APP towards the α-secretase pathway may have a beneficial effect in lowering Aβ peptide levels.



The characterization of APP secretases during the past few years has provided significant advancement in therapeutic strategies that may lead to limiting the build up of A peptide in the brain and eliminate or delay the pathological effects of AD. Recent characterization of secretases has uncovered several common features, particularly their sensitivity to certain metalloproteinase inhibitors and up-regulation of their activity by phorbol esters. Presenilins and γ-secretases are considered to be the best molecular targets for developing therapeutic agents that may minimize the debilitating effects of AD. Major targets in AD research are identifying the genetic and environmental factors responsible for β-amyloid build-up in nerve cells.

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Secretase Inhibitors

Product Name	Cat. No.	Comments	Size
APP β-Secretase Inhibitor (H-KTEEISEVN-Stat-VAEF-OH)	**171601**	A potent inhibitor of the amyloid precursor protein (APP) β-secretase (IC_{50} = 30 nM).	500 µg
Bafilomycin A1, *Streptomyces griseus*	**196000**	A macrolide antibiotic that acts as a specific inhibitor of vacuolar-type H^+-ATPase (V-type; K_i = 500 pM) and is reported to selectively inhibit β-secretase.	10 µg
MG-132	**474790**	A potent, reversible, and cell-permeable proteasome inhibitor (K_i = 4 nM). Reduces the degradation of ubiquitin-conjugated proteins in mammalian cells and permeable strains of yeast by the 26S complex without affecting its ATPase or isopeptidase activities. Blocks the maturation of APP Swedish mutant (APPSw) preventing cleavage by β-secretase. Inhibits NF-κB activation (IC_{50} = 3 µM).	1 mg 5 mg
OM99-2	**496000**	A peptidomimetic, highly potent, tight-binding transition-state analog inhibitor of β-secretase (K_i = 1.6 nM, recombinant memapsin-2; K_i = 9.58 nM, recombinant pro-memapsin 2). Designed from the template of the β-secretase site of Swedish β-amyloid precursor protein (APP) with Asp to Ala replacement.	250 µg
Pepstatin A Methyl Ester	**516485**	A cell-permeable methyl ester derivative of Pepstatin A (Cat. No. 516481) that acts as a potent, non-competitive transition-state analog inhibitor of γ-secretase (K_{is} = 150 nM, K_{ii} = 320 nM for human γ-secretase at 20°C; K_{is} is the inhibition constant for inhibitor binding to the free enzyme and K_{ii} is the inhibition constant for inhibitor binding to the Enzyme-Substrate complex).	1 mg 5 mg
β-Secretase Inhibitor II (Z-VLL-CHO)	**565749**	A potent, cell-permeable, and reversible inhibitor of β-secretase. Corresponds to the β-secretase cleavage site (VNL-DA) of the Swedish mutant Amyloid Precursor Protein (APP). Inhibits the formation of both $Aβ_{total}$(IC_{50} = 700 nM) and $Aβ_{1-42}$ (IC_{50} = 2.5 µM) in Chinese hamster ovary (CHO) cells transfected with wild-type APP751.	1 mg 5 mg
β-Secretase Inhibitor III	**565780**	A substrate analog inhibitor of β-secretase (BACE) that completely blocks the proteolytic activity (at 5 µM) in solubilized membrane fractions from BACE transfected MDCK cells.	500 µg
γ-Secretase Inhibitor I (Z-LLNle-CHO)	**565750**	Inhibits γ-secretase activity.	1 mg
γ-Secretase Inhibitor II	**565755**	A reversible and selective peptidomimetic inhibitor of γ-secretase (IC_{50} = 13 µM for total inhibition of Aβ). Displays only weak inhibitory activity against calpain II (IC_{50} = 100 µM in a purified enzyme assay).	1 mg
γ-Secretase Inhibitor III (Z-LL-CHO)	**565760**	A cell-permeable, specific, and reversible inhibitor of γ-secretase that reduces the formation of both $Aβ_{total}$ (IC_{50} ~35 µM) and $Aβ_{1-42}$ in Chinese hamster ovary (CHO) cultures stably transfected with amyloid precursor protein-751. Reported to be nontoxic in nature.	1 mg 5 mg
γ-Secretase Inhibitor IV (2-Naphthoyl-VF-CHO)	**565761**	A cell-permeable, reversible inhibitor of γ-secretase. Inhibits the release of $Aβ_{x-40}$ (ED_{50} = 2.6 µM) and $Aβ_{x-42}$ (ED_{50} = 2.7 µM) in HEK293 cells stably transfected with the APP Swedish mutants.	1 mg
γ-Secretase Inhibitor V (Z-LF-CHO)	**565762**	A cell-permeable, reversible inhibitor of γ-secretase. Reported to inhibit the release of $Aβ_{x-40}$ (ED_{50} = 5.0 µM) in HEK293 cells stably transfected with the APP Swedish mutants.	1 mg
γ-Secretase Inhibitor VI [1-(S)-*endo*-N-(1,3,3)-Trimethylbicyclo[2.2.1]hept-2yl-4-fluorophenyl Sulfonamide]	**565763**	A cell-permeable inhibitor of $Aβ_{42}$ production (IC_{50} = 1.8 µM). Treatment of HEK293 cells with this inhibitor results in an increase in β-secretase-cleaved APP fragments and secreted $APP_sα$.	5 mg
γ-Secretase Inhibitor VII (MOC-LL-CHO)	**565768**	A cell-permeable, reversible inhibitor of Aβ and p3 secretion ($Aβ_{40}$ IC_{50} = 2.3 µM; $Aβ_{42}$ IC_{50} = 3 µM). Reported to be more potent (IC_{50} = 900 nM and 740 nM for $Aβ_{40}$ and $Aβ_{42}$, respectively) in the presence of C99 inhibitor (10 µM).	1 mg
γ-Secretase Inhibitor IX (DAPT)	**565770**	A cell-permeable dipeptide that reduces Aβ production by blocking γ-secretase ($Aβ_{total}$ IC_{50} = 115 nM, $Aβ_{42}$ IC_{50} = 200 nM). Reported to be functionally active in both HEK293 cells and neuronal cultures without affecting the secretion of amyloid-β precursor protein.	5 mg

Secretase Inhibitors, *continued*

Product Name	Cat. No.	Comments	Size
γ-Secretase Inhibitor X (L-685,458)	**565771**	A cell-permeable, highly specific and potent inhibitor of γ-secretase ($A\beta_{total}$ IC_{50} = 17 nM, $A\beta_{40}$ IC_{50} = 48 nM, and $A\beta_{42}$ IC_{50} = 67 nM in SH-SY5Y cells overexpressing spβA4CTF). Binds to presenilin and blocks Notch intracellular domain production. Functions as a transition state analog mimic at the catalytic site of an aspartyl protease. Exhibits over 100-fold greater selectivity for γ-secretase than for cathepsin D.	250 µg
γ-Secretase Inhibitor XI (7-Amido-4-chloro-3-methoxyisocoumarin)	**565772**	An active site-directed, irreversible serine protease inhibitor that acts as a highly selective, potent inhibitor of γ-secretase. Blocks production of both amyloid-β_{40} ($A\beta_{40}$) and $A\beta_{42}$ (IC_{50} <100 µM) in HEK293 cells expressing wild-type and Swedish mutant β-amyloid precursor protein.	5 mg
γ-Secretase Inhibitor XII (Z-IL-CHO)	**565773**	A cell-permeable, reversible dipeptide aldehyde that reduces Aβ production by blocking γ-secretase *in vitro* ($A\beta_{40}$ IC_{50} = 7.9 µM; $A\beta_{42}$ IC_{50} = 7.6 µM) and in cultured CHO cells that stably overexpress APP695 ($A\beta_{40}$ IC_{50} = 11.5 µM; $A\beta_{42}$ IC_{50} = 8.3 µM). Also blocks the generation of γ CTF (γ-secretase-generated C-terminal fragment). Does not affect the formation of amyloid-β precursor protein.	5 mg
γ-Secretase Inhibitor XIII (Z-YIL-CHO)	**565774**	A cell-permeable, reversible inhibitor of γ-secretase. In TPA-stimulated T47-14 cells, it abolishes nuclear localization of ErbB-4 receptor tyrosine kinase by inhibiting the formation of the s80 ErbB-4 fragment.	5 mg
γ-Secretase Inhibitor XIV [Z-C(t-Bu)-IL-CHO]	**565775**	A cell-permeable, reversible inhibitor of γ-secretase that reduces Aβ production ($A\beta_{40}$ IC_{50} = 190 nM; $A\beta_{42}$ IC_{50} = 780 nM) in solubilized membrane preparations and in cultured APP695 expressing CHO cells ($A\beta_{40}$ IC_{50} = 80 nM; $A\beta_{42}$ IC_{50} = 120 nM).	5 mg
γ-Secretase Inhibitor XVI (DAPM)	**565777**	A cell-permeable γ-secretase inhibitor with anti-aggregation property (Aβ IC_{50} ~10 nM in 7PA2 cells). Prevents early Aβ oligomerization by selectively blocking the Aβ dimer and trimer formation.	5 mg
γ-Secretase Inhibitor XVII (WPE-III-31C)	**565778**	A cell-permeable (hydroxyethyl)urea peptidomimetic that acts as a transition-state analog inhibitor of γ-secretase (IC_{50} = 300 nM for Aβ production in whole cells). Binds the presenilin-γ-secretase complex (PS1-NTF, PS1-CTF, Nicastrin, and C83 APP CTF).	500 µg
γ-Secretase Inhibitor XVIII (Compound E)	**565779**	A cell-permeable peptidyl dihydrobenzodiazepinone derivative that acts as a highly potent, selective, non-transition state and non-competitive inhibitor of γ-secretase (IC_{50} $A\beta_{total}$ = 300 pM in CHO cells overexpressing wild-type βAPP). Binds to the active site of PS1 and PS2.	250 µg
NEW γ-Secretase Inhibitor XIX	**565787**	A cell-permeable, highly potent γ-secretase inhibitor (IC_{50} = 60 pM towards $A\beta_{40}$ secretion in SH-SY5Y cells overexpressing spβA4CTF).	100 µg
γ_{40}-Secretase Inhibitor I (t-3,5-DMC-IL-CHO)	**565765**	A potent, cell-permeable, reversible inhibitor of γ-secretase that preferentially inhibits the secretion of $A\beta_{1-40}$ (> 90%) vs. $A\beta_{1-42}$ (~15%). IC_{50} = ~15 µM for $A\beta_{total}$; ~22 µM for $A\beta_{1-40}$; and > 50 µM for $A\beta_{1-42}$ in CHO cells stably transfected with the cDNA encoding βAPP695. Reported to be about 10-fold more potent than Z-Val-Phe-CHO (MDL 28170; Cat. No. 208722).	1 mg
γ_{40}-Secretase Inhibitor II (BOC-GVV-CHO)	**565766**	A cell-permeable, substrate-based (γ_{40}-site) γ-secretase inhibitor that is reported to preferentially (> 90%) inhibit Aβ cleavage at site 40 vs. 42, in a dose-dependent fashion, in transiently transfected 293T cells over-expressing APP695NL.	1 mg 5 mg

Nitric Oxide/Oxidative Stress

Arginase Inhibitors

Arginase, an Mn^{2+} metalloenzyme, catalyzes the hydrolysis of L-arginine to yield L-ornithine and urea in ureotelic animals. Based on their distribution, two isoforms of arginase have been described. Type I arginase, a cytosolic enzyme, is found in the hepatic tissue and besides participating in the urea cycle, it also plays a significant role in limiting the supply of arginine for nitric oxide (•NO) synthesis. Type II arginase is a mitochondrial enzyme found in extrahepatic tissues, and is involved in the regulation of extra-urea cycle arginine metabolism and in the down-regulation of NO synthesis.

Due to the reciprocal regulation between arginase and nitric oxide synthase, arginase inhibitors are considered to have therapeutic potential in treating NO-dependent smooth muscle disorders, such as erectile dysfunctions and polyamine induced bronchial constriction.

References:

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Salimuddin et al. 1999. *Am J. Physiol. Endocrinol. Metab.* **277,** E110.
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Arginase Inhibitors

Product	Cat. No.	Comments	Size
BEC, Hydrochloride	**197900**	A slow-binding, competitive transition state inhibitor of arginase I and II (K_i = 313 nM for human recombinant type II arginase).	5 mg
N^{ω}-Hydroxy-nor-L-arginine, Diacetate Salt	**399275**	A potent, selective, competitive, and high affinity inhibitor of arginase (IC_{50} = 2 μM for rat liver arginase).	1 mg 5 mg
DL-α-Difluoromethylornithine, Hydrochloride	**288500**	An arginase inhibitor that potentiates vasodilatory effects of adenosine and also acts as an irreversible inhibitor of ornithine decarboxylase.	25 mg

Glutathione S-Transferase (GST) Inhibitors

Glutathione S-transferases (GST) constitute a family of phase II detoxification isozymes that catalyze the conjugation of glutathione with a number of hydrophobic compounds. Due to high expression of GSTs in tumors compared to normal tissues and their high level in plasma from cancer patients, these enzymes are considered to be cancer markers. All species possess multiple cytosolic and membrane-bound GST isozymes. These isozymes differ in their tissue-specific expression and distribution. They provide protection to mammalian cells against the toxic and neoplastic effects of electrophilic metabolites of carcinogens and reactive oxygen species.

Increased expression of GST isozymes has been linked to the development of resistance to alkylating cytostatic drugs. Their deficiency reportedly increases predisposition to various forms of cancer. Hence, GST status may be a useful prognostic factor to determine the clinical outcome of chemotherapy.

References:

Wu, Z., et al. 2004. *J. Med. Chem.* **47,** 3282.
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Kolm, R.H., et al. 1995. *Biochem. J.* **311,** 453.
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Glutathione S-Transferase Inhibitors

Product	Cat. No.	Comments	Size
Caffeic Acid	**205546**	An effective irreversible inhibitor of glutathione S-transferases and a non-competitive inhibitor of xanthine oxidase. Also acts as a selective, non-competitive inhibitor of 5-lipoxygenase (ID_{50} = 3.7 μM).	500 mg
Luteolin	**440025**	An antioxidant flavonoid and a free radical scavenger that is shown to inhibit rat liver cytosolic glutathione S-transferase activity.	5 mg

Guanylate Cyclase Inhibitors

Guanylyl cyclase (GC) catalyzes the formation of the second messenger cyclic GMP (cGMP) from GTP. cGMP-signaling is mediated by cGMP-activated protein kinases, the cGMP-regulated phosphodiesterases and the cGMP-gated ion channels. The action of cGMP is terminated by the action of cGMP-degrading phosphodiesterases. GC is present either as soluble (sGC) or as membrane-bound enzyme linked to a receptor. sGC is activated by another second messenger, nitric oxide (NO). Membrane-bound GC, on the other hand, is activated by hormones. The prosthetic heme group of sGC acts as the NO sensor, and binding of NO induces conformational changes leading to an up to 200-fold activation of the enzyme. The organic nitrates commonly used in the therapy of coronary heart disease exert their effects via stimulation of this enzyme. Two isoforms of the NO-sensitive heterodimeric enzyme have been identified, the ubiquitous $\alpha1\beta1$ isoform and the less broadly distributed $\alpha2\beta1$ isoform. These two forms differ in their subcellular distribution.

Membrane-bound GCs are receptor-linked enzymes with one membrane-spanning region. Although all of these GCs share a conserved intracellular catalytic domain, they differ in their extracellular ligand-binding domains and are activated by different peptide hormones. The guanylyl cyclase A (GC-A) isoform acts as the receptor for the natriuretic peptides, ANP and BNP, and hormones that are involved in the regulation of blood pressure as well as in the water and electrolyte household. GC-B is mainly found in the vascular endothelium and is thought to participate in smooth muscle relaxation. It displays the highest affinity for the natriuretic peptide of the C-type (CNP). GC-C is reported to bind the peptide hormone guanylin found in the intestine, where it is involved in salt and water balance. GC-C is stimulated by the heat-stable enterotoxin produced by *E. coli*.

References:

Friebe, A., and Koesling, D. 2003. *Cir. Res.* **93,** 96.
Denninger, J.W., and Marletta M.A. 1999. *Biochim. Biophys. Acta* **1411,** 334.
Russwurm, M., and Koesling, D. 2002. *Mol. Cell Biochem.* **230,** 159.
Koesling, D., and Friebe, A. 1999. *Rev. Physiol. Biochem. Pharmacol.* **135,** 35.

Guanylyl Cyclase Inhibitor Set

A set of 4 vials. Ech set contains 5 mg of LY 83583 (Cat. No. 440205); 1 g of Methylene Blue (Cat. No. 457250); 10 mg of ODQ (Cat. No. 495320); and 25 mg of Zinc (II) Protoporphyrin IX (Cat. No. 691550).

Cat. No. 371713 **1 Set**

Guanylate Cyclase Inhibitors

Product	Cat. No.	Comments	Size
Ambroxol, Hydrochloride	**129870**	A mucoactive and surfactant-stimulatory antioxidant that acts as a scavenger of hypochlorous and hydroxyl radicals. Blocks nitric oxide-stimulated activation of guanylate cyclase (IC_{50} ~2 - 4 μM).	1 g
LY 83583	**440205**	A competitive inhibitor of soluble guanylate cyclase (IC_{50} = 2 μM). Lowers the production of cGMP levels in a wide range of tissues by blocking intracellular Ca^{2+} release, with negligible effect on cAMP levels. Inhibits nitric oxide-induced smooth muscle relaxation.	5 mg 25 mg
Methylene Blue	**457250**	An inhibitor of soluble guanylate cyclase that acts as an organic spin-trap. Forms stable adducts with oxygen free radicals in solution.	1 g
NS 2028	**492030**	A potent, specific, and irreversible inhibitor of soluble guanylyl cyclase (IC_{50} = 30 nM for basal and 200 nM for NO-stimulated enzyme activity; IC_{50} = 17 nM for S-nitrosoglutathione-enhanced soluble guanylyl cyclase activity in homogenates of mouse cerebellum).	5 mg
ODQ	**495320**	A potent and selective inhibitor of nitric oxide (NO)-sensitive guanylyl cyclase (IC_{50} = 20 nM). In cerebellum slices, ODQ is shown to reversibly inhibit the NO-dependent cGMP response to glutamate receptor agonists without affecting NOS activity.	10 mg

Nitric Oxide Synthase (iNOS, bNOS, eNOS) Inhibitors

Nitric oxide (•NO), a highly reactive, diffusible, and unstable radical, plays an important role in the regulation of a wide range of physiological processes, including cellular immunity, angiogenesis, neurotransmission, and platelet aggregation. •NO is synthesized from L-arginine by the action of nitric oxide synthase (NOS) in a two-step oxidation process. Free •NO is a transient species with a half-life of only about five seconds. Hence, most studies on •NO action are based on the activity of NOS. •NO can diffuse across the cell membrane and react with a variety of targets. Reaction of •NO with O_2 in aqueous solutions produces the relatively unreactive nitrate and nitrite ions as products. However, •NO can rapidly react with superoxide to produce highly reactive peroxynitrite ($ONOO^-$). Almost all biological effects of •NO are achieved either directly or through other reactive nitrogen intermediates.

NOS is known to exist in three isoforms: (a) a soluble constitutively expressed enzyme found in high concentrations in the brain (bNOS; nNOS; or NOS-1), (b) a constitutively expressed endothelial membrane bound enzyme (eNOS, NOS-3), and (c) an inducible enzyme (iNOS or NOS-2) that is associated with the cytotoxic function of macrophages. These three isoforms exhibit similarities in their structure and mechanism of action. Calmodulin is required for the activity of all three isoforms. The activation of the constitutively expressed isoforms requires Ca^{2+}-dependent binding of calmodulin to the enzyme. However, in the case of iNOS, calmodulin is irreversibly bound to the enzyme and its activity is regulated by its rate of synthesis rather than by Ca^{2+} concentration. In the absence of calmodulin iNOS is highly unstable. For their catalytic activities NOS isoforms require three distinct domains: (a) a reductase domain, (b) a calmodulin-binding domain, and (c) an oxygenase domain. The reductase domain contains the FAD and FMN moieties. The oxygenase domain, which contains the binding sites for heme, tetrahydrobiopterin, and arginine, catalyzes the conversion of L-arginine to citrulline and •NO. The maximal rate of •NO synthesis is established by the intrinsic maximum ability of the reductase domain to deliver electrons to the heme domain.

Because of the involvement of all the three NOS isozymes in various aspects of signal transduction, NOS inhibitors have gained prominence in the management of ischemic reperfusion injury, hypotensive effects of drugs, and inflammatory response to cytokines.

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Chu, C.J., et al. 2000. *Clin Sci.* **99,** 475.
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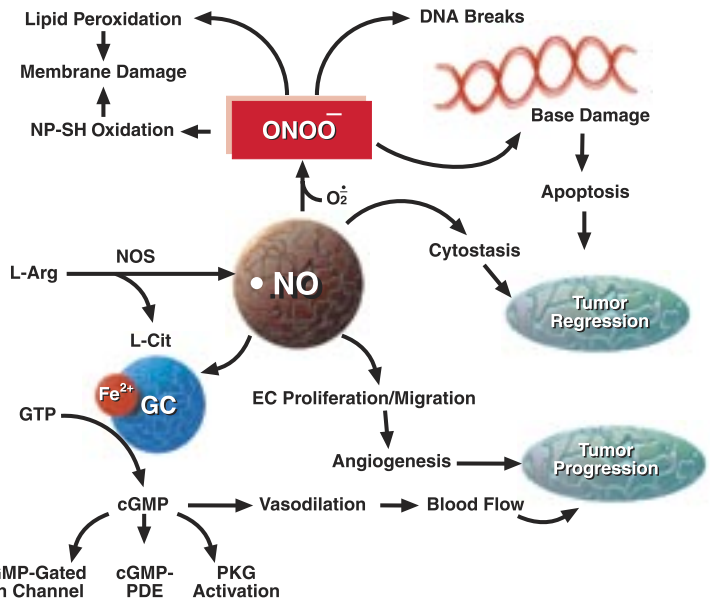

Table 2: Characteristics of various forms of Nitric Oxide Synthases

Enzyme	Gene	Number of Residues	Cellular Localization and Expression	Regulation
nNOS	*NOS1*	1429-1433	Brain: mainly soluble Skeletal muscle: mainly particulate	Ca^{2+}/CaM
iNOS	*NOS2*	1144-1153	Variety of cells: mainly soluble	Cytokine-inducible Ca^{2+}-independent
eNOS	*NOS3*	1203-1205	Vascular endothelial cells and cardiomyocytes: mainly particulate	Ca^{2+}/CaM

Table 3: Biological Activities of Selected Nitric Oxide Synthase Inhibitors (IC_{50}, K_i, and K_d values in μM)

Product	Cat. No.	eNOS	iNOS	bNOS
1400W	**100050**	50◊	0.007◊	2◊
S-Ethyl-N-phenylisothiourea, Hydrogen Iodide	**341170**	0.40*	0.87*	0.12*
2-Ethyl-2-thiopseudourea, Hydrobromide	**341180**	0.036*	0.017*	0.029*
L-N^5-(1-Iminoethyl)ornithine, Dihydrochloride	**400600**	0.5	2.2	3.9
S-Methylisothiourea Sulfate (SMT)	**466220**	–	2.0ǂ	–
S-Methyl-L-thiocitrulline, Dihydrochloride	**472804**	5.4	34	0.3
N^G-Monomethyl-L-arginine, Monoacetate (L-NMMA)	**475886**	0.7	3.9	0.65
L-NIL, Dihydrochloride	**482100**	–	3.3	92
N^G-Nitro-L-arginine (L-NNA)	**483120**	0.09*	8.1*	0.025*
7-Nitroindazole	**483400**	0.8	20	0.71
7-Nitroindazole, 3-Bromo-	**203911**	0.29	0.86	0.17
nNOS Inhibitor I	**490070**	314*	39*	0.12*
nNOS Inhibitor II	**490071**	195*	25*	0.13*
1,3-PBITU, Dihydrobromide	**512774**	9*	0.047*	0.25*
L-Thiocitrulline, Dihydrochloride	**589411**	–	3.6*	0.06*
N^G-Propyl-L-arginine	**537200**	8.5	180	0.057
TRIM	**643500**	>1000	27	28.2

Key: bNOS = brain nitric oxide synthase; eNOS = endothelial nitric oxide synthase; iNOS = inducible nitric oxide synthase.
Note: ◊ = K_d; * = K_i; ǂ = EC_{50}

Nitric Oxide Synthase (NOS) Inhibitors

Product	Cat. No.	Comments	Size
1400W	**100050**	A selective, irreversible, slow, tight binding inhibitor of iNOS (K_d = 7 nM) both *in vitro* and *in vivo*.	5 mg
1400W, Immobilized	**100051**	An immobilized form of the iNOS inhibitor (Cat. No. 100050) covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. Useful to affinity-precipitate NOS and other functionally related proteins from cell lysates and tissue extracts.	1 set
1-Amino-2-hydroxyguanidine, *p*-Toluenesulfate	**155200**	A potent inhibitor of iNOS in murine macrophages (IC_{50} = 68 μM) and rat aortic smooth muscle cells (RASM) in culture (IC_{50} = 114 μM).	10 mg
Dexamethasone	**265005**	Inhibits the expression of inducible but not constitutive NOS in vascular endothelial cells (IC_{50} = 5 nM).	100 mg
N^G,N^G-Dimethyl-L-arginine, Dihydrochloride	**311203**	Endogenous reversible inhibitor of nitric oxide synthesis *in vitro* and *in vivo*.	25 mg
Diphenyleneiodonium Chloride	**300260**	An irreversible inhibitor of eNOS (IC_{50} = 5 nM in macrophages).	10 mg
S-Ethyl-N-phenylisothiourea, Hydrogen Iodide	**341170**	A potent, competitive inhibitor of all three isoforms of human NOS. Displays the highest activity toward the nNOS (K_i = 870 nM for iNOS, 400 nM for eNOS, and 120 nM for nNOS).	25 mg
2-Ethyl-2-thiopseudourea, Hydrobromide	**341180**	A highly potent competitive inhibitor of human inducible (K_i = 17 nM), endothelial (K_i = 36 nM), and neuronal (K_i =29 nM) NOS isozymes.	100 mg
L-N^5-(1-Iminoethyl)ornithine, Dihydrochloride	**400600**	A potent inhibitor of eNOS (IC_{50} = 500 nM).	20 mg
MEG, Hydrochloride	**444600**	A cell-permeable inhibitor of iNOS and a peroxynitrite scavenger.	10 mg
S-Methyl-L-thiocitrulline, Dihydrochloride	**472804**	An inhibitor of NOS that exhibits about 17-fold greater selectivity for rat nNOS (IC_{50} = 300 nM) compared to the eNOS (IC_{50} = 5.4 μM).	10 mg
S-Methylisothiourea Sulfate	**466220**	A highly selective inhibitor of iNOS. Reported to be 10-30 fold more potent than L-NMMA (Cat. No. 475886) as an inhibitor of iNOS in immunostimulated cultured macrophages (EC_{50} = 6 μM) and vascular smooth muscle cells (EC_{50} = 2 μM).	100 mg
N^G-Monoethyl-L-arginine, Monoacetate Salt	**475883**	A nitric oxide synthase (NOS) inhibitor (K_i = 81 μM for iNOS; K_i = 66 μM for cNOS).	10 mg
N^G-Monomethyl-D-arginine, Monoacetate Salt	**475892**	A negative control for N^G-Monomethyl-L-arginine (Cat. No. 475886). May be used to investigate non-specific L-NMMA activity. Does not have any significant effect on nitric oxide synthase.	10 mg 25 mg 100 mg
N^G-Monomethyl-L-arginine, Monoacetate Salt	**475886**	An L-arginine analog that acts as a competitive inhibitor of all three isoforms of NOS (IC_{50} = 650 nM for nNOS; IC_{50} = 700 nM for eNOS; IC_{50} = 3.9 μM for iNOS).	25 mg 50 mg 100 mg
N^G-Monomethyl-L-arginine, *p*-Hydroxyazobenzene-*p*′-sulfonate Salt, Monohydrate	**475891**	A novel inhibitor of rat nNOS (IC_{50} = 3.3 μM). Inhibits histamine- and acetylcholine-induced relaxation of norepinephrine-constricted pulmonary artery.	25 mg
L-NIL, Dihydrochloride	**482100**	A potent and selective NOS inhibitor that exhibits greater selectivity for iNOS (IC_{50} = 3.3 μM) compared to nNOS (IC_{50} = 92 μM).	10 mg
nNOS Inhibitor I	**490070**	A potent and highly selective inhibitor of nNOS (K_i = 120 nM). Displays >2,500-fold and 192-fold selectivity over eNOS and iNOS, respectively.	1 mg 5 mg
nNOS Inhibitor II	**490071**	A potent and highly selective inhibitor of nNOS (K_i = 130 nM). Displays >1,500-fold and 192-fold selectivity over eNOS and iNOS, respectively.	1 mg 5 mg
N^G-Nitro-L-arginine (L-NNA)	**483120**	A potent, reversible inhibitor of bNOS (K_i = 25 nM) and eNOS (K_i = 90 nM.	100 mg
p-Nitroblue Tetrazolium Chloride	**484235**	NADPH-diaphorase substrate that competitively inhibits NOS (IC_{50} = 3-4 μM).	250 mg 1 g
7-Nitroindazole	**483400**	A reversible and competitive inhibitor of nitric oxide synthase (NOS) with high selectivity for the bNOS (IC_{50} = 710 nM). Also inhibits bovine eNOS (IC_{50} = 800 nM). Binds to the heme group of NOS.	100 mg
7-Nitroindazole, Sodium Salt	**484500**	A more soluble form of 7-Nitroindazole (Cat. No. 483400). Its solubility in artificial cerebrospinal fluid (CSF) permits its use as an inhibitor of nitric oxide synthase in brain tissue.	10 mg

Nitric Oxide Synthase (NOS) Inhibitors, *continued*

Product	Cat. No.	Comments	Size
7-Nitroindazole, 3-Bromo-	**203911**	Exhibits greater inhibitory activity than 7-Nitroindazole (Cat. No. 483400) on rat cerebellar nitric oxide synthase (NOS) isoforms (IC_{50} = 170 nM versus 710 nM) and rat lung NOS isoforms (IC_{50} = 290 nM versus 5.8 μM).	10 mg
1,3-PBITU, Dihydrobromide	**512774**	A highly potent competitive inhibitor of human nitric oxide synthase (NOS). Exhibits approximately 200 fold higher selectivity for iNOS (K_i = 47 nM) compared to eNOS (K_i = 9.0 μM).	50 mg
PPM-18	**529570**	A cell-permeable naphthoquinone derivative that inhibits the expression of iNOS (IC_{50} ~5 μM) by blocking the activation of NF-κB *in vitro* and *in vivo*. Does not directly affect the enzymatic activities of iNOS or eNOS.	10 mg
N^G-Propyl-L-arginine	**537200**	A potent, competitive, and time-dependent inhibitor of nNOS (K_i = 57 nM for nNOS; K_i = 180 μM for iNOS; K_i = 8.5 μM for eNOS).	5 mg
1-Pyrrolidinecarbodithioic Acid, Ammonium Salt	**548000**	Inhibits the induction of nitric oxide synthase activity in rat alveolar macrophages.	100 mg
SKF-525A, Hydrochloride	**567300**	Inhibits neuronal nitric oxide synthase (IC_{50} = 90 μM).	1 g
L-Thiocitrulline, Dihydrochloride	**589411**	A potent inhibitor of nNOS (K_i = 60 nM) compared to iNOS (K_i = 3.6 μM).	10 mg
TRIM	**643500**	A potent inhibitor of nNOS (IC_{50} = 28.2 μM) and iNOS (IC_{50} = 27.0 μM), however, it is a weak inhibitor of eNOS (IC_{50} = 1.06 μM).	100 mg

Also Available ...

Nitric Oxide Assay Kit, Colorimetric

Cat. No. 482650 1 kit

Nitric Oxide Assay Kit, Fluorometric

Cat. No. 482655 1 kit

Nitric Oxide Synthase Assay Kit

Cat. No. 482700 1 kit

Nitric Oxide Synthase Assay Kit, Colorimetric

Cat. No. 482702 1 kit

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Nitric Oxide Synthase, Inducible, Inhibitor Set

Provided as a 5 vial set. Each set contains 5 mg of 1400W (Cat. No. 100050); 10 mg of 1-Amino-2-hydroxyguanidine, *p*-Toluenesulfonate (Cat. No. 155200); 100 mg of S-Methylisothiourea Sulfate (Cat. No. 466220); 10 mg of L-NIL, Dihydrochloride (Cat. No. 482100); and 50 mg of 1,3-PBITU, Dihydrobromide (Cat. No. 512774).

Cat. No. 482760 1 set

Nitric Oxide Synthase, Neuronal, Inhibitor Set

Provided as a 4 vial set. Each set contains 100 mg of 7-Nitroindazole (Cat. No. 483400); 100 mg of N^G-Nitro-L-arginine (Cat. No. 483120); 10 mg of S-Methyl-L-thiocitrulline, Dihydrochloride (Cat. No. 472804); and 10 mg of L-Thiocitrulline, Dihydrochloride (Cat. No. 589411).

Cat. No. 482762 1 set

Proteases

Calpain Inhibitors

Calpains are a family of calcium-dependent thiol-proteases that proteolyze a wide variety of cytoskeletal, membrane-associated, and regulatory proteins. There are two major isoforms: calpain I (μ-form) and calpain II (m-form), which differ in their calcium requirement for activation. Calpains are heterodimers of 80-kDa and 30-kDa subunits. The 80-kDa unit has a catalytic site, which is unique to each isozyme, whereas the 30-kDa unit is the regulatory subunit and is common to both μ- and m-isozymes. The 80-kDa subunit consists of four domains (I-IV) and the 30-kDa unit has 2 domains (V and VI). Domain I is partially removed during autolysis. Domain II is the protease domain. Domain III exhibits homology with typical calmodulin binding proteins and interacts with calcium-binding domains (IV and VI) and frees the domain II for protease activity. Domain V contains a hydrophobic region that is essential for calpain interaction with membranes.

More recently, attention has been focused on the pathological significance of calcium accumulation in the central nervous system following cerebral ischemia and traumatic brain injury. Over-expression of NMDA, kainate, and AMPA receptors in the brain can lead to sustained influx of Ca^{2+} through voltage-gated Ca^{2+} channels. Disturbances in Ca^{2+} homeostasis results in the activation of several Ca^{2+}-dependent enzymes, including calpains.

Over-expression of calpains has been positively linked to both acute and chronic neurodegenerative processes including ischemia, trauma, and Alzheimer's disease. Calpain-mediated proteolysis is usually the late-stage common pathway towards cell death induced by excitotoxic compounds; hence, a selective inhibition of calpains to limit neuronal damage appears to be a viable therapeutic measure.

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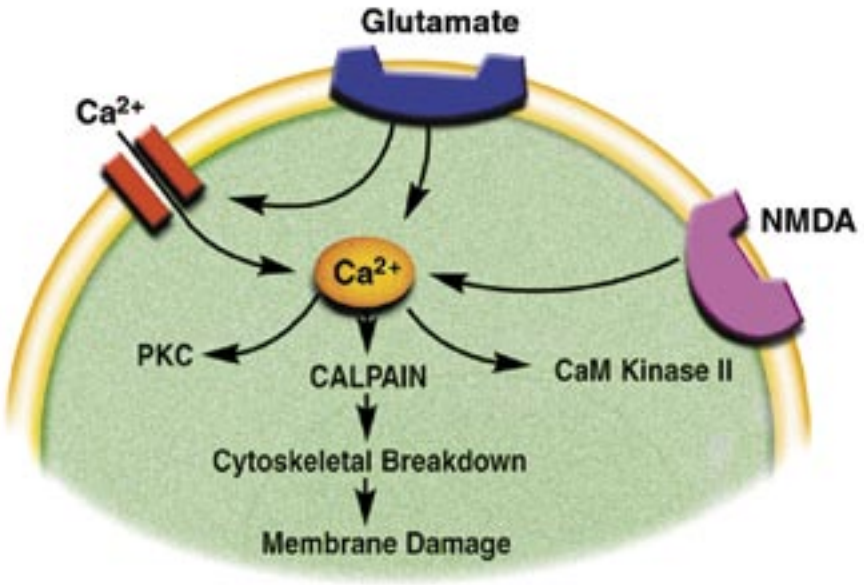


Calpain Inhibitors

Product	Cat. No.	Comments	Size
ALLM	**208721**	A cell-permeable inhibitor of calpain I (K_i = 120 nM), calpain II (K_i = 230 nM), cathepsin B (K_i = 100 nM), and cathepsin L (K_i = 600 pM).	25 mg
ALLN	**208719**	Inhibitor of calpain I (K_i = 190 nM), calpain II (K_i = 220 nM), cathepsin B (K_i = 150 nM), and cathepsin L (K_i = 500 pM).	5 mg 25 mg
ALLN in Solution	**208750**	A 10 mM solution of ALLN.	5 mg
Calpain Inhibitor III	**208722**	A potent, cell-permeable inhibitor of calpain I and II (K_i = 8 nM).	25 mg
Calpain Inhibitor IV	**208724**	A potent, cell-permeable and irreversible inhibitor of calpain II (k_2 = 28,900 $M^{-1}s^{-1}$).	1 mg
Calpain Inhibitor V	**208726**	A potent, non-selective, cell-permeable, and irreversible inhibitor of calpain (~100 µM).	1 mg
Calpain Inhibitor VI	**208745**	A cell-permeable, potent, and reversible inhibitor of calpain I (IC_{50} = 7.5 nM) and calpain II (IC_{50} = 78 nM).	1 mg 5 mg
Calpain Inhibitor VII	**433698**	A cell-permeable inhibitor of both calpain I and II.	5 mg
Calpain Inhibitor X	**208742**	A cell-permeable, potent, reversible, active site inhibitor of calpain I and calpain II (K_i ~250 nM).	1 mg 5 mg
Calpain Inhibitor XI	**208743**	A cell-permeable, potent, highly selective, reversible, active site inhibitor of calpain I (K_i = 140 nM) and calpain-2 (K_i = 41 nM).	1 mg 5 mg
Calpain Inhibitor XII	**208744**	A cell-permeable, potent, highly selective, reversible, active site inhibitor of calpain I (K_i = 19 nM) and calpain II (K_i = 120 nM).	1 mg 5 mg
Calpastatin, Human, Recombinant, Domain I	**208900**	An endogenous protease inhibitor that acts specifically on calpain I. Has greater inhibitory action compared to ALLM and ALLN. Not available for sale in Japan.	1 mg 3 mg
Calpastatin Peptide	**208902**	A cell-permeable and potent inhibitor of calpain I and calpain II (IC_{50} = 20 nM for purified rabbit calpain II).	500 µg
Calpastatin Peptide, Negative Control	**208904**	A scrambled peptide with an identical amino acid composition to that of Calpastatin Peptide (Cat. No. 208902). Useful as a negative control for Calpastatin Peptide.	500 µg
Calpeptin	**03-34-0051**	A cell-permeable inhibitor of calpain I (ID_{50} = 52 nM), calpain II (ID_{50} = 34 nM), and papain (ID_{50} = 138 nM).	5 mg 25 mg 100 mg
EST	**330005**	A cell-permeable, irreversible inhibitor of cysteine proteases that is reported to block the activation of calpain I.	1 mg
PD 145305	**513021**	A useful negative control for the calpain inhibitors PD 150606 (Cat. No. 513022) and PD 151746 (Cat. No. 513024).	1 mg
PD 150606	**513022**	A cell-permeable, selective non-peptide calpain inhibitor (K_i = 210 nM for calpain I and 370 nM for calpain II) directed towards the calcium-binding sites of calpain.	5 mg
PD 151746	**513024**	A cell-permeable, non-peptidic, and highly selective calpain inhibitor that displays over 20-fold greater selectivity for calpain I (K_i = 260 nM) over calpain II (K_i = 5.33 µM).	2 mg

Calpain Inhibitor Set

Provided as a 5 vial set. Each set contains 5 mg ALLN (Cat. No. 208719); 25 mg Calpain Inhibitor III (Cat. No. 208722); 5 mg of Calpeptin (Cat. No. 03-34-0051); 1 mg of EST (Cat. No. 330005); and 5 mg of PD 150606 (Cat. No. 513022).

Cat. No. 208733 **1 set**

Collagenase Inhibitors (Also see Matrix Metalloproteinase Inhibitors)

Mammalian collagenases belong to the family of metalloproteinases that specifically cleave collagen. On a dry weight basis collagen constitutes over 70% of skin weight. Collagenases have a unique ability to degrade native collagen that is normally resistant to breakdown by other proteases. They catalyze a single proteolytic cleavage in the helical collagen chains, resulting in two fragments that are subsequently accessible to less specific proteases. Collagenases are produced by macrophages, fibroblasts, and keratinocytes that are involved in the wound-healing process. In normal healthy subjects, even during wound healing, the activity of endogenous collagenases is low and is sufficient for the removal of dead tissue. However, in patients with chronic nonhealing wounds and ulcers, there may be impairment of endogenous collagenase production leading to insufficient removal of dead tissue. Such conditions warrant the application of bacterial collagenases to clean the wound and begin the healing process. Collagenases also play an important role in separating cells from their anchors. They dissolve desmosomes and thereby enable cells to migrate on a matrix of fibronectin. Fibroblast migration also requires these proteases to enable them to move within the wound.

Collagenase Inhibitors

Product	Cat. No.	Comments	Size
Collagenase Inhibitor I	**234140**	A potent and specific inhibitor of vertebrate collagenases (IC_{50} = 1 μM).	5 mg
TAPI-0	**579050**	A hydroxymate-based inhibitor of collagenase, gelatinase, and TACE [TNF-α convertase; ADAM17 (IC_{50} = 100 nM)].	1 mg
TAPI-1	**579051**	A structural analog of TAPI-0 (Cat. No. 579050) with similar *in vitro* efficacy for the inhibition of MMPs and TACE.	1 mg

Elastase Inhibitors

Elastases are serine proteases that hydrolyze amides and esters. They are distinctive in their action upon elastin. Because elastin is found in highest concentrations in the elastic fibers of connective tissues, elastase is frequently used to dissociate tissues that contain extensive intercellular fiber networks. For this purpose they are used in association with other enzymes such as collagenase, trypsin, and chymotrypsin.

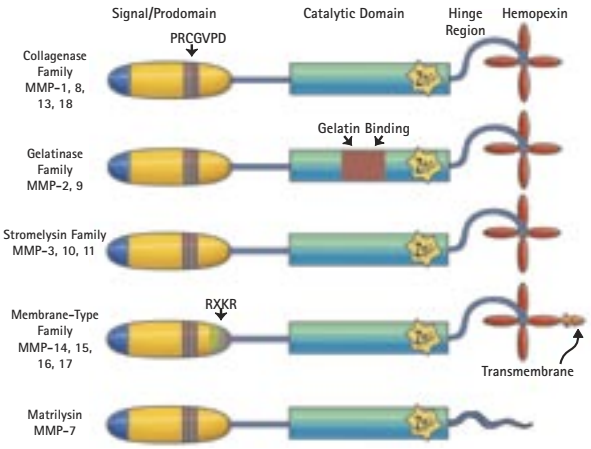
Elastase is also found in blood components and this enzyme is identical to pancreatic elastase, but differs from the elastase of polymorphonuclear leukocytes. The leukocyte enzyme, which is inhibited by α_1-antitrypsin but not by pancreatic trypsin inhibitor, is known to mediate pathological elastolysis during acute arthritis and pulmonary emphysema.

Elastase Inhibitors

Product	Cat. No.	Comments	Size
α_1-Antitrypsin, Human Plasma	**178251**	An inhibitor of neutrophil elastase, cathepsin G, and proteinase 3.	1 mg 5 mg
Caffeic Acid	**205546**	An inhibitor of neutrophil elastase (IC_{50} = 93 μM). Also acts as a selective, non-competitive inhibitor of 5-lipoxygenase (ID_{50} = 3.7 μM), glutathione S-transferases, and xanthine oxidase.	500 mg
Cholesterol Estrase Inhibitor	**228205**	A serine protease inhibitor that acts as a competitive, active site directed, alternate substrate inhibitor of bovine pancreatic CEase (K_i = 580 nM). Also inhibits human leukocyte elastase (K_i = 13 nM).	5 mg
Elastase Inhibitor I	**324692**	A serine protease inhibitor that inhibits porcine pancreatic elastase (PPE; $k_i = 128\ M^{-1}sec^{-1}$) and thermitase ($k_i = 1.14 \times 10^3\ M^{-1}sec^{-1}$).	1 mg
Elastase Inhibitor II	**324744**	A potent inhibitor of human neutrophil elastase (HNE). The inhibition results from cross-linking of catalytic residues His^{57} and Ser^{195}.	5 mg
Elastase Inhibitor III	**324745**	A potent inhibitor of human leukocyte elastase (HLE) (K_i = 10 μM).	5 mg

Matrix Metalloproteinase (MMP) Inhibitors

The proteolytic degradation of the extracellular matrix (ECM) by tumor cells requires the action of highly specialized MMPs that are expressed in cell- or tissue-specific patterns. MMPs also play an important role in wound healing, angiogenesis, embryogenesis, and in pathological processes such as tumor invasion and metastasis. MMPs are characterized by the presence of a zinc ion in the active site, which is required for their catalytic activity. Thus far 28 different types of MMPs (secreted or transmembrane enzymes) have been identified and classified based on their protein domain structures derived from genomic data. Of these, 23 MMPs have been found to be expressed in human tissues. Secreted MMPs include minimal-domain MMPs, simple hemopexin domain-containing MMPs, gelatin-binding MMPs, furin-activated MMPs, and vitronectin-like insert MMPs. The membrane-bound MMPs include type I transmembrane MMPs, glycosyl-phosphatidyl inositol (GPI)-linked MMPs, and type II transmembrane MMPs *(please see table below)*.



All MMPs sequenced to date have at least three domains in common. The prodomain contains a highly conserved segment of eight amino acids that folds over to cover the catalytic site and helps to maintain the inactive conformation following the release of MMPs. Cleavage of the prodomain destabilizes the inhibitory interaction between the unpaired cysteine in the sequence and the active site zinc. The catalytic domain contains the conserved structural metal-binding sites consisting of 106 to 119 residues. MMPs also contain a highly conserved zinc-binding active site domain containing 52 to 58 amino acids. The zinc-binding domain contains three His residues that occupy three of the coordination sites of the active site Zn^{2+}. In addition to these, the hemopexin-like domain found in all MMPs (except MMP-7) plays a role in substrate specificity.

The activation of MMPs is dependent mainly on urokinase-type (uPA) and tissue-type (tPA) plasminogen activators that cleave plasminogen into active plasmin. A major control point in the regulation of active enzyme is inhibition of the active form by the TIMP family of inhibitors (21-28 kDa). TIMPs regulate the function of MMPs either by inhibiting active MMPs or by controlling their activation process. They form tight, non-covalent inhibitory complexes with MMPs (K_d = 10 to 50 pM).

MMPs facilitate tumor cell invasion and metastasis by at least three distinct mechanisms: (a) by eradicating physical barriers to invasion through degradation of collagens, laminins, and proteoglycans in the ECM, (b) by modulating cell adhesion and enabling cells to form new cell-to-cell and cell-to-matrix attachments while breaking the existing ones, and (c) by acting on ECM components and other proteins to expose hidden biological activities, such as release of angiostatin from plasminogen. In normal adults, MMP expression is very low except in rapidly remodeling tissue, such as wound healing and menstrual endometrium. Many control elements, such as secretion of MMPs in their latent form and the presence of TIMPs, tend to keep MMPs inactive in the ECM.

Table 4: Matrix Metalloproteinase (MMP)

Group	MMP
Simple Hemopexin Domain-Containing MMPs	MMP-1, MMP-3, MMP-8, MMP-10, MMP-12, MMP-13, MMP-18, MMP-19, MMP-20, MMP-22, and MMP-27
Gelatin-Binding MMPs	MMP-2 and MMP-9
Furin-Activated Secreted MMPs	MMP-11 and MMP-28
Vitronectin-Like Insert MMPs	MMP-21
Minimal Domain MMPs	MMP-7 and MMP-26
GPI-linked MMPs	MMP-17 and MMP-25
Type I Transmembrane MMPs	MMP-14, MMP-15, MMP-16, and MMP-24
Type II Transmembrane MMPs	MMP-23

Matrix Metalloproteinase Inhibitors

Product	Cat. No.	Comments	Size
CL- 82198	**233105**	A selective inhibitor of MMP-13 (IC_{50} = 10 μM) that does not appear to act by chelating Zn^{2+}. Binds within the entire S1′ pocket of MMP-13, docking with the morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	5 mg
GM 1489	**364200**	A potent broad-spectrum inhibitor of MMPs. Inhibits MMPs *in vitro* (K_i = 200 pM for MMP-1; K_i = 500 nM for MMP-2; K_i = 20 μM for MMP-3; K_i = 100 nM for MMP-8; K_i = 100 nM for MMP-9).	1 mg 5 mg
GM 6001	**364205**	A potent broad-spectrum hydroxamic acid inhibitor of MMPs. Inhibits MMPs *in vitro* (K_i = 400 pM for skin fibroblast MMP-1; K_i = 500 pM for MMP-2; K_i = 27 nM for MMP-3; K_i = 0.1 nM for MMP-8; and K_i = 200 pM for MMP-9).	1 mg 5 mg
GM 6001, Negative Control	**364210**	A useful negative control for the MMP inhibitor GM 6001 (Cat. No. 364205).	1 mg 5 mg
MMP Inhibitor I	**444250**	An inhibitor of MMP-1 and MMP-8 (IC_{50} = 1.0 μM), MMP-9 (IC_{50} = 30 μM), and MMP-3 (IC_{50} = 150 μM).	10 mg
MMP Inhibitor II	**444247**	An inhibitor of MMP-1 (IC_{50} = 24 nM), MMP-3 (IC_{50} = 18.4 nM), MMP-7 (IC_{50} = 30 nM), and MMP-9 (IC_{50} = 2.7 nM).	1 mg
MMP Inhibitor III	**444264**	A Homophenylalanine-hydroxamic acid based broad spectrum inhibitor of MMPs. Inhibits MMP-1 (IC_{50} = 7.4 nM), MMP-2 (IC_{50} = 2.3 nM), MMP-3 (IC_{50} = 135 nM), MMP-7 (IC_{50} = 10 - 100 nM), and MMP-13 (IC_{50} = 1 -10 nM).	1 mg
MMP Inhibitor IV	**444271**	A peptide hydroxamic acid that inhibits MMPs and pseudolysin from P. *aeruginosa* (~500 nM).	5 mg
MMP-2 Inhibitor I	**444244**	A potent inhibitor of MMP-2 ((K_i = 1.7 μM).	10 mg
MMP-2/MMP-3 Inhibitor I	**444239**	A potent inhibitor of MMP-2 (K_i = 17 μM) and MMP-3 (K_i = 290 nM).	5 mg
MMP-2/MMP-3 Inhibitor II	**444240**	A potent inhibitor of MMP-2 (K_i = 4.5 μM) and MMP-3 (K_i = 520 nM).	2 mg
MMP-2/MMP-9 Inhibitor I	**444241**	A potent inhibitor of MMP-2 (IC_{50} = 310 nM) and MMP-9 (IC_{50} = 240 nM).	5 mg
MMP-2/MMP-9 Inhibitor II	**444249**	A potent inhibitor of type IV collagenases, MMP-2 (IC_{50} = 17 nM) and MMP-9 (IC_{50} = 30 nM).	1 mg
MMP-2/MMP-9 Inhibitor III	**444251**	A cyclic peptide that acts as a potent inhibitor of MMP-2 (IC_{50} = 10 μM) and MMP-9 (IC_{50} = 10 μM). Inhibits the migration of human endothelial cells and tumor cells, and prevents tumor growth and invasion in animal models.	1 mg
MMP-2/MMP-9 Inhibitor IV	**444274**	A potent, selective, slow-binding and mechanism-based inhibitor of human MMP-2 (K_i = 13.9 nM) and MMP-9 (K_i = 600 nM). Does not affect the activities of MMP-1 (K_i = 206 μM) MMP-3 (K_i = 15 μM), or MMP-7 (K_i = 96 μM).	500 μg
MMP-3 Inhibitor I	**444218**	An inhibitor of MMP-3 (IC_{50} = 5 μM). Based on a segment from the conserved region of the N-terminal propeptide domain.	5 mg
MMP-3 Inhibitor II	**444225**	A potent inhibitor of human MMP-3 (K_i = 130 nM).	5 mg
MMP-3 Inhibitor III	**444242**	A potent inhibitor of MMP-3 (K_i = 3.2 μM) that inhibits MMP-2 only at higher concentrations (K_i >200 μM).	2 mg
MMP-3 Inhibitor IV	**444243**	A potent inhibitor of MMP-3 (K_i = 810 nM) that inhibits MMP-2 only at higher concentrations (K_i >200 μM).	2 mg
MMP-3 Inhibitor V	**444260**	A potent and competitive inhibitor of MMP-3. Inhibits both human and rabbit MMP-3 (wild type and mutants) with K_i values in the low μM range.	5 mg
MMP-3 Inhibitor VI	**444265**	A potent and competitive inhibitor of MMP-3. Inhibits both human and rabbit MMP-3 (wild type and mutants) with K_i values in the low μM range.	5 mg
NEW MMP-3 Inhibitor VII	**444280**	A potent nonpeptide inhibitor of MMP-3 (stromelysin; IC_{50} = 25 nM against the catalytic domain).	1 mg
NEW MMP-3 Inhibitor VIII	**444281**	A cell-permeable, potent inhibitor of human MMP-3 (stromelysin; K_i = 23 nM) and murine macrophage metalloelastase (MME/MMP-12; IC_{50} = 13 nM).	5 mg
MMP-8 Inhibitor I	**444237**	A potent inhibitor of MMP-8 (IC_{50} = 4 nM).	1 mg
MMP-8 Inhibitor I, Negative Control	**444238**	A negative control for MMP-8 Inhibitor I (Cat. No. 444237; IC_{50} = 1 μM).	1 mg
MMP-9 Inhibitor I	**444278**	A potent and selective inhibitor of MMP-9 (IC_{50} = 5 nM). Inhibits MMP-1 (IC_{50} = 1.05 μM) and MMP-13 (IC_{50} = 113 nM) only at much higher concentrations	500 μg
MMP-9/MMP-13 Inhibitor I	**444252**	A piperazine-based potent inhibitor of MMP-9 (IC_{50} = 900 pM) and MMP-13 (IC_{50} = 900 pM). Inhibits MMP-1 and MMP-3 at much higher concentrations (IC_{50} = 43 nM and 23 nM, respectively). Also acts as an inhibitor of MMP-7(IC_{50} = 930 nM).	1 mg
MMP-9/MMP-13 Inhibitor II	**444253**	A piperazine-based potent inhibitor of MMP-9 (IC_{50} = 1.9 nM) and MMP-13 (IC_{50} = 1.3 nM). Inhibits MMP-1 and MMP-3 at higher concentrations (IC_{50} = 24 nM and 18 nM, respectively). Also acts as a weak inhibitor of MMP-7 (IC_{50} = 230 nM).	1 mg

Tissue Inhibitors of Matrix Metalloproteinases (TIMPs)

Tissue inhibitors of metalloproteinases (TIMPs) are a family of endogenous inhibitors that regulate the activation and activity of MMPs. They have been shown in animal models to be capable of the inhibition of tumor cell invasion and metastasis. They may also be involved in other diseases such as arthritis and periodontal disease. TIMP-1 is a 184 amino-acid glycoprotein of 28.5 kDa. TIMP-1 preferentially binds and inhibits MMP-9 and MMP-1 through interaction with their catalytic domains. TIMP-2 is a 194 amino acid, non-glycosylated protein of 21 kDa with 43% and 44% homology to TIMP-1 and TIMP-3, respectively. It inhibits the activity of all active MMPs and regulates MMP-2 expression by binding to the C-terminal region of pro-MMP-2 (K_d ~5 nM). As with TIMP-1, TIMP-2 has been shown to have erythroid-potentiating activity and cell growth-promoting activity. TIMP-3 is present in the eye. It is tightly bound to the extracellular matrix and has been shown to inhibit TNF-α converting enzyme. A mutation in TIMP-3 is found in Sorsby's fundus dystrophy, a dominantly-inherited form of blindness. TIMP-4 blocks the activities of several matrix metalloproteinases (MMPs) implicated in the arthritic cartilage erosion.

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Tissue Inhibitors of Matrix Metalloproteinases

Product	Cat. No.	Comments	Size
TIMP-1, Recombinant, Bovine	**PF020**	A CHO cell-derived protein. Shown to inhibit MMP-1 (IC_{50} = 1-5 nM). Not available for sale in Japan.	3 µg
TIMP-1, Human Neutrophil Granulocyte	**612080**	A 28 kDa glycoprotein that forms a non-covalent stochiometric complex with latent and active MMPs. Binds to pro-MMP-9 and MMP-9 via their C-terminal domains.	5 µg
TIMP-1, Recombinant, Human	**PF019**	A 28 kDa glycoprotein that is expressed by a variety of cell types. It forms a non-covalent, stoichiometric complex with both latent and active MMPs. TIMP-1 preferentially binds and inhibits MMP-9. Not available for sale in Japan.	3 µg
TIMP-2, Human Rheumatoid Synovial Fibroblast	**612084**	Forms a non-covalent stoichiometric complex with latent and active MMPs. Shown to inhibit the activities of MMP-1, MMP-2, MMP-12, and transin.	5 µg
TIMP-2, Recombinant, Human	**PF021**	A 21 kDa (nonreduced) or a 24 kDa (reduced) protein expressed by a variety of cell types. Forms a non-covalent, stoichiometric complex with both latent and active MMPs. TIMP-2 preferentially binds and inhibits MMP-2. Not available for sale in Japan.	3 µg
TIMP-2, Mouse, Recombinant	**PF098**	A 194 amino acid non-glycosylated protein with 43% and 44% homology to TIMP-1 and TIMP-3, respectively. Inhibits the activity of all MMPs and regulates MMP-2 expression by binding to the C-terminal region of pro-MMP-2. TIMP-2 is constitutively produced by most cell types in culture, along with MMP-2.	5 µg
TIMP-3, Human, Recombinant	**PF095**	Constitutively produced by many cell types. Differs from the other TIMPs in its localization to the extracellular matrix. TIMP-3 has a more basic K_i than the other TIMPs, and the basic residues are thought to help anchor TIMP-3 into the ECM.	5 µg
TIMP-3, Mouse, Recombinant	**PF096**	Constitutively produced by many cell types in culture. Differs from the other TIMPs in its localization to the extracellular matrix. Has a more basic K_i than the other TIMPs, and the basic residues are thought to help anchor TIMP-3 into the ECM. TIMP-3 is an efficient "sheddase" inhibitor, inhibiting ADAM-17 (TACE) at the low nanomolar levels.	5 µg
TIMP-4, Human Fibroblast	**PF097**	Binds to Gelatinase A in manner similar to TIMP-2. Overexpression of TIMP-4 is reported to inhibit cell invasiveness *in vitro*.	5 µg

Protease Inhibitors

The proper functioning of the cell requires an optimum level of important structural proteins, enzymes, and regulatory proteins. One mechanism whereby cells achieve this steady state level is by proteolytic degradation. Peptidases (proteases) can be subdivided into two major groups: the endopeptidases and the exopeptidases, which cleave peptide bonds either at points within the protein or remove amino acids sequentially from either the N- or C-terminus, respectively. The term proteinase is also used as a synonym for endopeptidase. The International Union of Biochemistry and Molecular Biology has recognized four classes of proteases: serine proteinases, cysteine proteinases, aspartic proteinases, and metalloproteinases.

In vivo, proteins are either protected in specialized compartments or they reside in a special protective conformation. Every protein isolated from cells is a potential substrate for proteolytic enzymes. Protease inhibitors are often used in experimental protocols that require extraction and analysis of intact proteins. These inhibitors block the activity of proteases and minimize tissue damage during purification procedures and organ perfusion studies. More recently, selected protease inhibitors have been used as anti-HIV agents.

Several commonly used protease inhibitors are either synthetic or of bacterial or fungal origin. They inhibit protease activity in either a reversible or irreversible manner. Over 100 naturally occurring protease inhibitors have been identified so far. They behave as tight-binding reversible or pseudo-irreversible protease inhibitors preventing substrate access to the active site through steric hindrance. Some of them act by modifying an amino acid residue of the protease active site. For example, serine proteases are inactivated by phenylmethane sulfonyl fluoride (PMSF), which reacts with the active site serine, whereas the chloromethylketone derivatives react with the histidine of the catalytic triad.

Protease Inhibitors

Product	Cat. No.	Comments	Size
Acetyl-Pepstatin	**110175**	An aspartyl protease inhibitor that acts as an effective inhibitor of HIV-1 proteinase (K_i = 20 nM at pH 4.7).	1 mg
AEBSF, Hydrochloride	**101500**	Water-soluble, non-toxic alternative to PMSF. Irreversible inhibitor of serine proteases. Reacts covalently with a component of the active site. Inhibits chymotrypsin, kallikrein, plasmin, trypsin, and related thrombolytic enzymes.	50 mg 100 mg 500 mg 1 g
AEBSF, Immobilized	**101501**	An immobilized form of the protease inhibitor AEBSF (Cat. No. 101500) covalently attached to hydrophobic acrylic beads. Useful as a scavenger for serine proteases where the interfering protease-inhibitor complex can be easily removed.	50 mg
ALLN	**208719**	Inhibitor of calpain I (K_i = 190 nM), calpain II (K_i = 220 nM), cathepsin B (K_i = 150 nM), and cathepsin L (K_i = 500 pM).	5 mg 25 mg
ALLM	**208721**	Inhibitor of calpain I (K_i = 120 nM), calpain II (K_i = 230 nM), cathepsin B (K_i = 100 nM), and cathepsin L (K_i = 600 pM).	25 mg
Amastatin, *Streptomyces sp.*	**129875**	Binds to cell surfaces and reversibly inhibits aminopeptidases. A slow binding, competitive inhibitor of aminopeptidase M and leucine aminopeptidase. Has no significant effect on aminopeptidase B.	1 mg
ε-Amino-*n*-caproic Acid (EACA)	**1381**	A lysine analog that inhibits carboxypeptidase B. Promotes rapid dissociation of plasmin by inhibiting the activation of plasminogen.	500 g
α_1-Antichymotrypsin, Human Plasma	**178196**	An acute phase plasma protein that functions as a specific inhibitor of chymotrypsin-like serine proteases.	100 µg 1 mg
α_2-Antiplasmin, Human Plasma	**178221**	An inhibitor of plasminogen-activator-induced lysis of fibrin clots. Forms a covalent complex with plasmin and inactivates it.	100 µg
Antipain, Dihydrochloride	**178223**	Peptidyl arginine aldehyde protease inhibitor produced by actinomycetes. Inhibitor of Ca^{2+}-dependent endopeptidases. Has specificity similar to Leupeptin (Cat. No. 108975). Inhibits trypsin-like serine proteases, papain and some cysteine proteases (IC_{50} = 300 µM).	5 mg 10 mg
Antipain, Hydrochloride	**178220**	A reversible inhibitor of cysteine and serine proteases.	5 mg 10 mg

Protease Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Antithrombin III, Human Plasma	**169756**	Complexes with serine proteases of blood coagulation system including thrombin, plasmin, kallikrein, and factors IXa, Xa, XIa, and XIIa. Potency is strongly enhanced in the presence of heparin.	1 mg
α_1-Antitrypsin, Human Plasma	**178251**	A serine protease inhibitor that also acts as a major physiological regulator of elastase.	1 mg 5 mg
p-APMSF, Hydrochloride	**178281**	A specific irreversible inhibitor of trypsin-like serine proteases. A suitable alternative to DFP and PMSF.	5 mg
Aprotinin, Bovine Lung, Agarose Conjugate	**178487**	Aprotinin (Cat. No. 616398) immobilized on beaded agarose at 7000 KIU/ml. Useful for the purification of serine proteases.	2 ml
Aprotinin, Bovine Lung, Biotinylated	**616415**	The biotinylated form of the Aprotinin (Cat. No. 616370). Useful as a sensitive probe for the detection of serine proteinases on immunoblots. Contains ≥3 moles of biotin per mole of aprotinin	50 µg
Aprotinin, Bovine Lung, Crystalline	**616370**	A competitive and reversible inhibitor of esterase and protease activity. Forms a tight complex with and blocks the active site of target enzymes. Inhibits a number of different proteases, including chymotrypsin, coagulation factors involved in the pre-phase of blood clotting, kallikrein (K_d = 1 x 10^{-7} M), plasmin (K_d = 2.3 x 10^{-10} M), tissue and leukocyte proteinases, and trypsin (K_d = 5 x 10^{-14} M).	10 mg 20 mg 100 mg
Aprotinin, Bovine Lung, Solution	**616399**	A competitive and reversible inhibitor of proteolytic and esterolytic activity. A serine protease inhibitor. In cell cultures, extends the life of cells and prevents proteolytic damage to intact cells.	100 KU 500 KU
ATBI, Synthetic	**189250**	A potent inhibitor of various aspartyl proteases. Shown to inhibit pepsin in a slow-tight binding, competitive manner (K_i = 55 pM). Also functions as a tight binding, non-competitive inhibitor of HIV-1 protease that functions at the active site of the flap region (K_i = 17.8 nM).	1 mg
Benzamidine, Hydrochloride	**199001**	Inhibitor of trypsin and trypsin-like enzymes. Benzamidine derivatives have been used in inhibiting the growth of colon carcinoma cells. Inhibits factor VII autoactivation.	5 g 25 g
Bestatin	**200484**	Binds to cell surfaces and inhibits cell surface aminopeptidases, notably aminopeptidase B and leucine aminopeptidase. Activates macrophages and T lymphocytes. Has antitumor properties.	10 mg
Bestatin, Methyl Ester	**200485**	A cell-permeable derivative of Bestatin (Cat. No. 200484) that displays slightly stronger inhibition of neutral aminopeptidase than Bestatin but has much weaker activity against basic aminopeptidase.	5 mg
Calpastatin, Human, Recombinant, Domain I	**208900**	A potent inhibitor of calpain, a Ca^{2+}-dependent cysteine protease. Has greater inhibitory action than calpain inhibitors I and II. Inhibitory sequence has 18 amino acid residues. Not available for sale in Japan.	1 mg 3 mg
CA-074	**205530**	A potent, irreversible inhibitor of Cathepsin B *in vivo* and *in vitro* (IC_{50} = 2.24 nM for rat liver cathepsin B).	1 mg
CA-074 Me	**205531**	Membrane-permeable analog of CA-074 (Cat. No. 205530) that acts as an inhibitor of intracellular cathepsin B.	1 mg
Calpeptin	**03-34-0051**	A cell-permeable calpain inhibitor. Inactivates calpain I (ID_{50} = 52 nM), calpain II (ID_{50} = 34 nM), and papain (ID_{50} = 138 nM).	5 mg 25 mg 100 mg
Carboxypeptidase Inhibitor, Potato	**217359**	A potent inhibitor of a wide variety of digestive tract carboxypeptidases. In immobilized form, suitable for the purification of carboxypeptidases.	5 mg
Cathepsin Inhibitor I (Z-Phe-Gly-NHO-Bz)	**219415**	Selectively inhibits cathepsin B (k_2/K_i = 8.9 x 10^3 M^{-1} sec^{-1}), cathepsin L (k_2/K_i = 3.8 x 10^5 M^{-1} sec^{-1}), cathepsin S (k_2/K_i = 4.2 x 10^4 M^{-1} sec^{-1}), and papain (k_2/K_i = 1.8 x 10^3 M^{-1} sec^{-1}).	1 mg
Cathepsin Inhibitor II (Z-Phe-Gly-NHO-Bz-pMe)	**219417**	Selectively inhibits cathepsin B (k_2/K_i = 6.9 x 10^3 M^{-1} sec^{-1}), cathepsin L (k_2/K_i = 3.1 x 10^5 M^{-1} sec^{-1}), cathepsin S (k_2/K_i = 6.6 x 10^4 M^{-1} sec^{-1}), and papain (k_2/K_i = 1.8 x 10^3 M^{-1} sec^{-1}).	1 mg
Cathepsin Inhibitor III (Z-Phe-Gly-NHO-Bz-pOMe)	**219419**	Cysteine protease inhibitor. Selectively inhibits cathepsin B (k_2/K_i= 1.0 x 10^4 M^{-1} sec^{-1}), cathepsin L (k_2/K_i = 1.5 x 10^5 M^{-1} sec^{-1}), cathepsin S (k_2/K_i = 6.6 x 10^4 M^{-1} sec^{-1}), and papain (k_2/K_i = 1.0 x 10^3 M^{-1} sec^{-1}).	1 mg
Cathepsin B Inhibitor I (Caspase Inhibitor Negative Control)	**342000**	A cathepsin B inhibitor. Also suitable as a negative control for caspase-1.	1 mg 5 mg

Protease Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Cathepsin B Inhibitor II (Ac-Leu-Val-Lysinal)	**219385**	A more active lysinal analog of leupeptin (Cat. No. 108975). Inhibits cathepsin B at nanomolar levels (IC_{50} = 4 nM).	1 mg
Cathepsin G Inhibitor I	**219372**	A potent, selective, reversible, and competitive non-peptide inhibitor of cathepsin G (IC_{50} = 53 nM and K_i = 63 nM).	1 mg
Cathepsin K Inhibitor I	**219377**	A cell-permeable, potent, selective, reversible inhibitor of cathepsin K (K_i = 22 nM). Binds to cathepsin K and span both the S- and S′- subsites.	5 mg
Cathepsin K Inhibitor II	**219379**	A cell-permeable, potent, selective, and reversible inhibitor of cathepsin K (K_i = 6 nM).	1 mg
Cathepsin K Inhibitor III	**219381**	A cell-permeable, potent, selective, reversible inhibitor of cathepsin K ($K_{i,app}$ = 9.7 nM). At higher concentrations also inhibits the activities of cathepsin L, cathepsin B, and papain ($K_{i,app}$ = 120 nM, 5.1 µM, and 2.3 µM, respectively).	1 mg
Cathepsin L Inhibitor I (Z-Phe-Phe-CH2F)	**219421**	A potent, cell-permeable, and irreversible inhibitor of cathepsins B and L.	1 mg
Cathepsin L Inhibitor II (Z-Phe-Tyr-CHO)	**219426**	A potent and selective inhibitor of cathepsin L.	5 mg
Cathepsin L Inhibitor III [Z-Phe-Tyr-(t-Bu)-CHN2]	**219427**	An irreversible cathepsin L inhibitor. About 10^4-fold more effective against cathepsin L (k_2/K_i = 2 x 10^5 $M^{-1}sec^{-1}$) than cathepsin S.	5 mg
Cathepsin L Inhibitor IV	**219433**	A potent inhibitor of cathepsin L (IC_{50} = 1.9 nM). Also inhibits the release of Ca^{2+} and hydroxyproline from bone in an *in vitro* bone culture system.	1 mg
Cathepsin L Inhibitor V	**219435**	A slow, tight-binding reversible inhibitor of recombinant human cathepsin L (K_i = 600 pM). Exhibits over 360-fold greater selectivity for cathepsin L compared to cathepsin B (K_i = 214 nM).	1 mg
Cathepsin L Inhibitor VI	**219495**	An end-protected tripeptide that acts as a highly selective, potent, and reversible inhibitor of human recombinant cathepsin-L (K_i = 19 nM).	5 mg
Cathepsin S Inhibitor	**219393**	A slow, tight-binding reversible inhibitor of recombinant cathepsin S (K_i = 185 pM). Exhibits over 410-fold greater selectivity for cathepsin S than for cathepsin B (K_i = 76 nM).	1 mg
Cathepsin/Subtilisin Inhibitor (Boc-Val-Phe-NHO-Bz-pCl)	**219420**	Inhibits members of the cysteine protease family including cathepsin L, and members of the serine protease family including subtilisin Carlsberg and thermitase.	1 mg
Chymostatin	**230790**	A reversible serine and cysteine protease inhibitor. Inhibits chymotrypsin-like serine proteases.	5 mg 10 mg 25 mg
Chymotrypsin Inhibitor I, Potato	**230906**	A pentamer consisting of 5 - 8 kDa monomeric subunits. Each subunit inhibits one molecule of chymotrypsin. Suppresses radiation transformation of C3H/10T1/2 cells *in vitro*.	10 mg
Cystatin, Egg White	**240891**	A competitive and reversible cysteine protease inhibitor.	500 µg
3,4-Dichloroisocoumarin	**287815**	A potent irreversible inhibitor of serine proteases. Reacts with serine proteases to release acyl chloride moiety that can acylate another active site residue. Has no action on thiol proteases and metalloproteases.	10 mg
Diisopropylfluorophosphate (DFP)	**30967**	A potent irreversible inhibitor of serine proteases. Also irreversibly inactivates acetylcholinesterase.	1 g
Dipeptidyl Peptidase IV Inhibitor I	**416200**	A serine protease inhibitor.	5 mg
Dipeptidyl Peptidase IV Inhibitor II [H-Glu-(NHO-Bz)-Pyr, HCl]	**317638**	A reversible inhibitor of dipeptidyl peptidase II (K_i = 3.8 µM) and dipeptidyl peptidase IV (K_i = 1.0 µM).	1 mg
1,5-DNS-GGACK, 2HCl	**251700**	An effective irreversible inhibitor of Factor Xa (IC_{50} = 100 nM) and urokinase.	5 mg
Dipeptidylpeptidase II Inhibitor	**317621**	A potent and highly specific inhibitor of dipeptidylpeptidase II (IC_{50} = 130 nM). Displays ~7,700-fold greater selectivity for human seminal fluid DPP II compared to DPP IV (IC_{50} >1 mM).	10 mg
E-64 Protease Inhibitor	**324890**	An irreversible cysteine protease inhibitor that has no action on cysteine residues in other proteins. Specific active site titrant.	1 mg 5 mg 25 mg

Protease Inhibitors, *continued*

Product	Cat. No.	Comments	Size
E-64, Immobilized	**324891**	An immobilized form of the cysteine protease inhibitor E-64 (Cat. No. 324890) covalently attached to hydrophilic acrylic beads via a 4-carbon spacer. Useful to affinity-precipitate cathepsins and other functionally related proteins from cell lysates or tissue extracts. Each set contains 25 mg of E-64 immobilized beads and 25 mg of control beads.	1 set
Ecotin, *E. coli*	**330200**	A potent, broad range inhibitor of serine proteases. Exhibits picomolar binding constant for the inhibition of chymotrypsin, elastase, Factor Xa Factor XIIa, kallikrein, and trypsin. Also an effective inhibitor of collagenase and Granzyme B.	100 µg
EDTA, Disodium Salt, Dihydrate Molecular Biology Grade	**324503**	A reversible metalloprotease inhibitor. A chelator that may interfere with other metal ion-dependent biological processes.	100 g 1 kg
EDTA, Tetrasodium Salt	**34103**	A reversible metalloprotease inhibitor. A chelator that may interfere with other metal ion-dependent biological processes.	500 g
EGTA	**324625**	A metalloprotease inhibitor. Highly useful for removal of heavy metal ions in biological systems.	1 g
EGTA, Molecular Biology Grade	**324626**	A metalloprotease inhibitor. Highly useful for removal of heavy metal ions in biological systems.	10 g 25 g
Elastase Inhibitor I (Boc-Ala-Ala-Ala-Na-NHO-Bz)	**324692**	A serine protease inhibitor that inhibits pancreatic elastase (K_i = 128 M^{-1} sec^{-1}) and thermitase.	1 mg
Elastase Inhibitor II (MeO-Sac-Ala-Ala-Pro-Ala-CMK)	**324744**	A potent inhibitor of human neutrophil elastase.	5 mg
Elastase Inhibitor III	**324745**	A potent inhibitor of human neutrophil elastase (K_i = 10 µM).	5 mg
Elastatinal	**324691**	A competitive inhibitor of elastase (K_i = 240 nM).	5 mg
EST (E-64d)	**330005**	A membrane permeable calpain inhibitor. Its action is similar to E-64 (Cat. No. 324890); however, it is devoid of charged groups.	1 mg
FUT-175	**344960**	A synthetic broad-specificity serine protease inhibitor. Potently inhibits both coagulation and complement proteinases (C3a, C4a, and C5a) as well as Granzyme A. Inhibits Factor VIIa-mediated, Factor Xa generation (IC_{50} = 100 nM).	5 mg
GGACK	**347436**	An irreversible inhibitor of urokinase (IC_{50} <1 µM) and Factor Xa.	5 mg
GGACK, Biotinylated, Dihydrochloride	**347437**	Biotin-X conjugate of Cat. No. 347435. Specific probe for active serine proteases. Potent inhibitor of Factor Xa.	1 mg
2-Guanidinoethylmercaptosuccinic Acid	**369334**	Potent inhibitor of a carboxypeptidase B-like processing enzyme referred to as enkephalin convertase (K_i = 8.8 nM). Ideal for use in affinity chromatography of the enzyme.	5 mg
HDSF	**373250**	A substrate analog of phenylmethylsulfonyl fluoride (PMSF) that acts as an irreversible inhibitor of the lysosomal lipolytic enzyme, palmitoyl-protein thioesterase-1 (PPT1) (IC_{50} = 125 µM) by modifying an active site serine (Ser^{115}) in the enzyme.	25 mg 100 mg
HIV Protease Inhibitor	**382135**	A potent HIV protease inhibitor (IC_{50} = 900 nM) that acts by binding to the active site of the HIV protease. Also inhibits cathepsin D (IC_{50} = 37 µM) and pepsin (IC_{50} = 100 µM) at high concentrations.	1 mg
α-Iodoacetamide	**407710**	An irreversible inhibitor of several cysteine proteases. Useful for alkylating cysteine and methionine residues.	25 g
Kininogen, High Molecular Weight, Single Chain, Human Plasma	**422686**	Synthesized as a single polypeptide chain in the liver and secreted into the plasma, where it complexes with prekallikrein and factor XI.	1 mg
Kininogen, High Molecular Weight, Two Chain, Human Plasma	**422688**	Two-chain kinin-free kininogen prepared by kallikrein digestion of kininogen, which is then re-purified to remove traces of kallikrein. Binds to papain and cathepsin S with high affinity, exhibiting 2:1 binding stoichiometry.	1 mg
Kininogen, Low Molecular Weight, Human Plasma	**422685**	A multi-functional plasma protein that functions as a cysteine protease inhibitor.	100 µg
Leuhistin	**432077**	Microbial product. Competitively inhibits aminopeptidase M (K_i = 230 nM).	5 mg
Leupeptin, Hemisulfate (Ac-Leu-Leu-Arginal)	**108975**	A reversible inhibitor of trypsin-like proteases and cysteine proteases.	5 mg 10 mg 25 mg 50 mg 100 mg

Protease Inhibitors, *continued*

Product	Cat. No.	Comments	Size
α_2-Macroglobulin, Human Plasma	**441251**	A broad-range irreversible protease inhibitor. Forms "trap" around most proteases.	1 mg 10 mg
DL-2-Mercaptomethyl-3-guanidinoethylthiopropanoic Acid (Plummer's Inhibitor)	**445825**	A potent and reversible inhibitor of human plasma carboxypeptidase N (K_i = 2 nM). Also inhibits the hydrolysis of bradykinin.	100 mg
NCO-700	**479919**	An epoxysuccinic acid derivative that acts as a specific cysteine protease inhibitor. Inhibits cathepsin B (IC_{50} = 800 nM), cathepsin L (IC_{50} = 67 µM), and papain (IC_{50} = 280 nM).	1 mg
α_1-PDX, Human, Recombinant, *E. coli*	**126850**	Recombinant protein derived from the bioengineered human a_1-antitrypsin gene fused to a His•Tag™ sequence and a FLAG®-tag. Contains a minimal furin consensus sequence, RXXR, that effectively blocks the furin-dependent processing of protein precursors (K_i = 600 pM).	2.5 mg
Pepstatin A, Synthetic	**516481**	A reversible inhibitor of aspartic proteases. Inhibits cathepsin D, pepsin, and renin.	5 mg 25 mg 100 mg 250 mg
Phenylmethylsulfonyl Fluoride (PMSF)	**52332**	An irreversible inhibitor of serine proteases. Its mechanism of action is analogous to that of diisopropylfluorophosphate. PMSF causes sulfonylation of the active-site serine residues.	1 g 5 g 25 g
Phosphoramidon, Disodium Salt	**525276**	A highly specific inhibitor of thermolysin. Inhibits the conversion of big endothelin-1 to endothelin (IC_{50} = 4.6 µM).	5 mg
PPACK, Biotinylated	**520224**	Biotin-X-analog of Cat. No. 520222. Specific probe for active serine proteases. Potent inhibitor of thrombin and tissue plasminogen activator (tPA). Useful for Western blot analyses of Factor VIIa, Factor XIa, thrombin and tPA.	1 mg
PPACK, Dihydrochloride (D-Phe-Pro-Arg-Chloro-methylketone, Dihydrochloride)	**520222**	A potent and selective inhibitor of thrombin. Specifically alkylates an active center histidine and thus is classified as an affinity label for thrombin.	5 mg 25 mg
PPACK, Trifluoroacetate Salt	**520219**	A potent and irreversible inhibitor of plasma and glandular kallikreins.	5 mg 25 mg
Prolyl Endopeptidase Inhibitor	**537010**	An inhibitor for the proline-specific peptidase prolylendopeptidase (K_i = 11.7 µM for bacterial PEP, 1000 nM for porcine PEP, and 30 nM for human PEP) that combines the efficacy of aminoacyl-pyrrolidides and the potential transacylating capability of diacylhydroxylamines.	1 mg
Prolyl Endopeptidase Inhibitor II	**537011**	A cell-permeable dipeptide aldehyde that acts as a specific, potent, slow and tight-binding transition state analog inhibitor of prolyl endopeptidase (K_i = 350 pM and 500 pM for mouse brain and human brain prolyl endopeptidase, respectively).	5 mg
2,4,5,7-Tetranitro-9-Fluorenone	**584340**	A highly selective, irreversible, cell-permeable inhibitor of cysteine proteinases. Reported to reversibly bind to human adenovirus cysteine proteinase (hAVCP) and papain (K_i = 3.09 µM and 9.24 µM, respectively) followed by irreversible inhibition of both enzymes.	250 mg
TLCK, Hydrochloride (Nα-Tosyl-Lys-Chloromethylketone, Hydrochloride)	**616382**	An irreversible inhibitor of trypsin-like serine proteases. Inactivates trypsin, specifically and irreversibly. Does not have any significant inhibitory effect on chymotrypsin.	50 mg 250 mg
Thrombin Inhibitor	**605200**	This peptide boronic acid compound that acts as a potent and selective inhibitor of thrombin (K_i = 7 nM).	5 mg
TPCK (Nα-Tosyl-Phe-Chloromethylketone)	**616387**	An irreversible inhibitor of chymotrypsin. Useful for inhibiting chymotrypsin activity in trypsin preparations.	250 mg 1 g
Tripeptidylpeptidase II Inhibitor	**645905**	A serine protease inhibitor that acts as a potent, selective, dose-dependent, and irreversible inhibitor of tripeptidylpeptidase II. Achieves about 80% inhibition of TPPII *in vitro* at 10 µM.	5 mg
Trypsin Inhibitor, Corn	**650345**	A specific inhibitor of human factor XIIa.	1 mg
Trypsin Inhibitor, Soybean	**65035**	A reversible serine protease inhibitor. Inhibits factor Xa, trypsin, chymotrypsin, kallikrein, and plasmin.	100 mg 1 g
Trypsin Inhibitor, Soybean, High Activity	**650357**	A reversible serine protease inhibitor. Inhibits factor Xa, trypsin chymotrypsin, kallikrein, and plasmin.	100 mg 250 mg

Protease Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Trypsin Inhibitor, Soybean, High Purity, Endotoxin-Free	**650358**	Endotoxins removed chromatographically. Inhibitor inactivates trypsin on an equimolar basis. Exhibits no effects on enzymatic activity of porcine pancreatic elastase.	25 mg 100 mg
Tyromycin A, Synthetic	**657005**	A cell-permeable citraconic anhydride derivative that inhibits the activities of leucine and cysteine aminopeptidases bound to the outer surface of HeLa S3 cells (IC_{50} = 20 μg/ml and 7 μg/ml, respectively). Also reported to inhibit carboxypeptidase A (IC_{50} = 60 μg/ml) at higher concentrations.	5 mg
D-Val-Phe-Lys Chloromethyl Ketone, Dihydrochloride (Plasmin Inhibitor)	**627624**	Selective irreversible inhibitor of plasmin with high selectivity for plasmin over urokinase.	5 mg
YO-2	**688190**	A selective plasmin inhibitor (IC_{50} ~500 nM for plasmin, ~30 μM for plasma kallikrein, ~5.3 μM for urokinase, >100 μM for thrombin).	5 mg

Protease Inhibitor Cocktail Set I

A cocktail containing five protease inhibitors that will inhibit a broad range of proteases. Reconstitute each vial with 1 ml H_2O to obtain a 100x stock solution. When diluted, 1x stock solution contains the following amount of inhibitors.

Cat. No. 539131 1 vial
10 vials

Product	Cat. No.	Mol. Wt.	1x Concentration	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	500 μM	Serine Proteases
Aprotinin	**616398**	6512	150 nM	Serine Proteases and Esterases
E-64 Protease Inhibitor	**324890**	357.4	1 μM	Cysteine Proteases
EDTA, Disodium	**324503**	372.2	0.5 mM	Metalloproteases
Leupeptin, Hemisulfate	**108975**	475.6	1 μM	Cysteine Proteases and Trypsin-like proteases

Protease Inhibitor Cocktail Set II

This cocktail is recommended for use with bacterial cell extracts. Cocktail contains five protease inhibitors with broad specificity for the inhibition of aspartic, cysteine, serine, and metalloproteases as well as aminopeptidases. Reconstitute each vial with 1 ml DMSO and 4 ml H_2O to obtain a 5 ml stock solution. When reconstituted each vial will contain the following amount of inhibitors. Note: 1 set = 1 vial of lyophilized protease inhibitor cocktail and 1 vial DMSO, 1 ml.

Cat. No. 539132 1 set
5 sets

Product	Cat. No.	Mol. Wt.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	20 mM	Serine Proteases
Bestatin	**200484**	308.4	1.7 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	357.4	200 μM	Cysteine Proteases
EDTA, Disodium	**324503**	372.2	85 mM	Metalloproteases
Pepstatin A	**516482**	685.9	2 mM	Aspartic Proteases

Note: contains EDTA, not recommended for immobilized affinity chromatography.

Protease Inhibitor Cocktail Set III

This cocktail is recommended for use with mammalian cells and tissue extracts. Cocktail contains six protease inhibitors (in 1 ml of DMSO) with broad specificity for the inhibition of aspartic, cysteine, and serine proteases as well as aminopeptidases. Each vial contains the following amount of inhibitors. One ml is sufficient for 20 g of tissue.

Cat. No. 539134 1 ml
1 set (5 x 1 ml)

Product	Cat. No.	Mol. Wt.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	100 mM	Serine Proteases
Aprotinin, Bovine Lung, Lyophilized	**616398**	6512	80 µM	Broad Spectrum, Serine Proteases
Bestatin	**200484**	308.4	5 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	357.4	1.5 mM	Cysteine Proteases
Leupeptin, Hemisulfate	**108975**	475.6	2 mM	Cysteine Proteases and Trypsin-like Proteases
Pepstatin A	**516482**	685.9	1 mM	Aspartic Proteases

Protease Inhibitor Cocktail Set IV

This cocktail is recommended for fungal and yeast cell extracts. Cocktail contains four protease inhibitors (in 1 ml of DMSO) with broad specificity for the inhibition of aspartic-, cysteine-, metallo-, and serine-proteases. Each vial contains the following amount of inhibitors.

Cat. No. 539136 1 set

Product	Cat. No.	Mol. Wt.	Concentration In the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	100 mM	Serine Proteases
E-64 Protease Inhibitor	**324890**	357.4	1.5 mM	Cysteine Proteases
Pepstatin A	**516482**	685.9	2 mM	Aspartic Proteases
o-Phenanthroline	**516705**	198.2	500 mM	Metalloproteases

Protease Inhibitor Cocktail Set V, EDTA-Free

A cocktail containing four protease inhibitors for the inhibition of serine, cysteine, but not metalloproteases. Reconstitute each vial with 1 ml H_2O to obtain a 100x stock solution. When diluted to 1x stock solution, the set will contain the following amount of inhibitors.

Cat. No. 539137 10 vials

Product	Cat. No.	Mol. Wt.	1x Concentration	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	500 µM	Serine Proteases
Aprotinin, Bovine Lung, Lyophilized	**616398**	6512	150 nM	Broad Spectrum, Serine Proteases
E-64 Protease Inhibitor	**324890**	357.4	1 µM	Cysteine Proteases
Leupeptin, Hemisulfate	**108975**	475.6	1 µM	Cysteine Proteases and Trypsin-like Proteases

Protease Inhibitor Cocktail Set VI

This cocktail is recommended for use with plant cell extracts. Cocktail contains six protease inhibitors (in 1 ml DMSO) with broad specificity for the inhibition of aspartic, cysteine, serine, and metalloproteases as well as aminopeptidases. Each vial contains the following amount of inhibitors. One ml is recommended for 30 g various plant tissues.

Cat. No. 539133 1 ml
1 set (5 x 1 ml)

Product	Cat. No.	Mol. Wt.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	200 mM	Serine Proteases
Bestatin	**200484**	308.4	10 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	357.4	3 mM	Cysteine Proteases
Leupeptin, Hemisulfate	**108975**	475.6	2 mM	Cysteine Proteases and Trypsin-like Proteases
o-Phenanthroline	**516705**	198.2	500 mM	Metalloproteases
Pepstatin A	**516482**	685.9	2 mM	Aspartic Proteases

Protease Inhibitor Cocktail Set VII

This cocktail is recommended for purification of proteins containing His•Tag™ sequences. Cocktail contains five protease inhibitors (in 1 ml DMSO) with broad specificity for the inhibition of cysteine, serine, aspartic, and thermolysin-like proteases and aminopeptidases. Each vial contains the following amount of inhibitors. One ml is recommended for the inhibition of proteases in 10 g cells.

Cat. No. 539138 1 ml
1 set (5 x 1 ml)

Product	Cat. No.	Mol. Wt.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	239.5	100 mM	Serine Proteases
Bestatin	**200484**	308.4	5 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	357.4	1.5 mM	Cysteine Proteases
Pepstatin A	**516482**	685.9	2 mM	Aspartic Proteases
Phosphoramidon	**525276**	587.5	0.2 mM	Metalloendopeptidases

NEW! Protease Inhibitor Cocktail Set VIII

A DMSO solution of three protease inhibitors with selective specificity for the inhibition of cysteine proteases, including calpains, cathepsins, and papain. Each vial contains 1.56 mM ALLN (Cat. No. 208719), 1.5 mM E64 Protease Inhibitor (Cat. No. 324890), and 500 µM Cathepsin Inhibitor I (Cat. No. 219415).

Cat. No. 539129 1 ml
1 Set (5 x 1 ml)

Protease Inhibitor Set

A set of 6 vials. Each set contains 50 mg of AEBSF, HCl (Cat. No. 101500), 1 mg of E-64 (Cat. No. 324890), 1 mg of EST (E-64d; Cat. No. 330005), 5 mg of Leupeptin, Hemisulfate (Cat. No. 108975), 5 mg of Pepstatin A (Cat. No. 516482), 50 mg of TLCK, HCl (Cat. No. 616382) and 250 mg of TPCK (Cat. No. 616387).

Cat. No. 539128 1 set

Protease Arrest™ Reagent

An optimized concentration of various reversible and irreversible inhibitors to inhibit serine, cysteine, and calpain proteases. Suitable for the protection of proteins purified from animal tissues, plant tissues, yeast, and bacteria. Protease Arrest™ Reagent is provided as a 50x solution that when diluted in extraction buffer at pH 7.0 - 8.0 inhibits 95 - 98% of protease activity. EDTA is also provided separately to inhibit metalloproteinases.

Cat. No. 539124 1 set

Serine Protease Inhibitor Cocktail Set I

A cocktail of four protease inhibitors that is useful for inhibition of a broad range of serine proteases. Reconstitute each vial with 1 ml of H_2O to obtain a 100x stock solution. 1x stock solution contains 500 µM AEBSF, HCl (Cat. No. 101500), 420 nM Aprotinin (Cat. No. 616398), 20 mM Elastatinal (Cat. No. 324691) and 1 mM GGACK (Cat. No. 347435).

Cat. No. 565000 1 vial
5 vials

Proteasome and Ubiquitination Inhibitors

Proteasomes are large multi-subunit complexes, localized in the nucleus and cytosol that selectively degrade intracellular proteins. A protein marked for degradation is covalently attached to multiple molecules of ubiquitin (Ubq). Four or more Ubq are required to set a protein for degradation by the proteasome. Ubq is a highly conserved 76-amino acid (8.6-kDa) protein, which escorts proteins for rapid hydrolysis to the multi-component enzymatic complex, the 26S proteasome. The proteolytic core of this complex, the 20S proteasome, contains multiple peptidase activities and functions as the catalytic machine. This core is composed of 28 subunits arranged in four heptameric, tightly stacked, rings (α_7, β_7, β_7, α_7) to form a cylindrical structure. The α-subunits make up the two outer and the β-subunits the two inner rings of the stack. The entrance of substrate proteins to the active site of the complex is guarded by the α-subunits that allow access only to unfolded and extended polypeptides. The proteolytic activity is confined to the β-subunits.

In the Ubq-proteosome degradation pathway, Ubq is first covalently ligated to target proteins by a multi-enzymatic system consisting of Ubq-activating (E1), Ubq-conjugating (E2), and the Ubq-ligating (E3) enzymes. The E1 activates a Ubq monomer at its C-terminal cysteine residue to a high-energy thioester bond which is then transferred to a reactive cysteine residue of the E2 enzyme. The final transfer of Ubq to the ε-amino group of a reactive lysine residue of substrate proteins is brought about by the E3 enzyme. Ubiquitinated protein is then escorted to the 26S proteasome where it undergoes final degradation and the ubiquitin is released and recycled.

The ubiquitin-proteasome system plays a major role in the degradation of many proteins involved in cell cycle, proliferation, and apoptosis. Proteasomes also breakdown abnormal proteins that result from oxidative stress and mutations that might otherwise disrupt normal cellular homeostasis. This pathway has been implicated in several forms of malignancy, in the pathogenesis of several genetic diseases, and in the pathology of muscle wasting. It is also involved in the destruction of proteins that participate in cell cycle progression, transcription control, signal transduction, and metabolic regulation.

Several distinct groups of compounds, designed to act as selective proteasome inhibitors, have helped immensely in understanding the biological role and importance of the ubiquitin-proteasome pathway. These compounds are designed to block proteasome function in cancer cells without significantly affecting biological processes in the normal cell.

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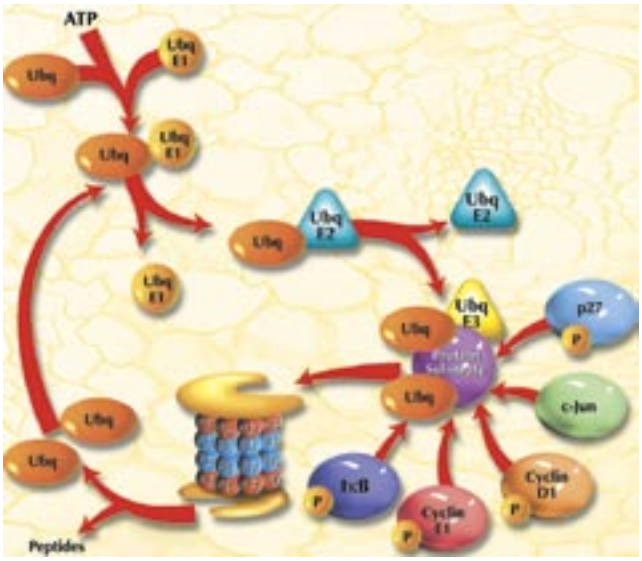

Proteasome and Ubiquitination Inhibitors

Product	Cat. No.	Cell-permeable?	Reversible?	Comments	Size
Aclacinomycin A, *Streptomyces galilaeus*	**112270**	–	Yes	An inhibitor of the chymotrypsin-like activity of the 20S proteasome (IC_{50} = ~52 μM).	50 mg
AdaAhX$_3$L$_3$VS	**114802**	Yes	No	Inhibits chymotrypsin-like (IC_{50} = 0.05 – 0.01 μM), trypsin-like (IC_{50} = 1.0 – 5.0 μM), and PGPH (IC_{50} = 0.5 – 1.0 μM) activities of the 20S proteasome.	250 μg
AdaLys(bio)AhX$_3$L$_3$VS	**114803**	Yes	No	Inhibits chymotrypsin-like (IC_{50} = 0.05 – 0.1 μM), trypsin-like (IC_{50} = 5.0 – 10.0 μM), and PGPH (IC_{50} = 2.0 – 5.0 μM) activities of the 20S proteasome in living cells. Useful for the detection of catalytic β-subunits of both constitutive proteasome and immunoproteasome through Western blotting.	250 μg
ALLN (Calpain Inhibitor I)	**208719**	Yes	Yes	Inhibits chymotrypsin-like activity of the proteasome (K_i = 5.7 μM). Also inhibits calpain I, calpain II, cathepsin B, and cathepsin L.	5 mg 25 mg
Epoxomicin, Synthetic	**324800**	Yes	No	Inhibits chymotrypsin-like, trypsin-like and peptidylglutamyl peptide hydrolyzing (PGPH) activities of the proteasome.	100 μg
NEW Hdm2 E3 Ligase Inhibitor	**373225**	Yes	Yes	A cell-permeable, reversible inhibitor of hdm2 E3 ligase that is shown to block hdm2-mediated ubiquitination of p53 (IC_{50} = 12.7 μM using Ub-Ubc4 as the donor substrate). The inhibition is non-competitive with respect to either the donor or acceptor substrate.	5 mg
Lactacystin, Synthetic	**426100**	Yes	No	A potent and selective proteasome inhibitor. Inhibits the chymotryptic-and tryptic-like peptidase activities of proteasomes. Also inhibits cathepsin A.	200 μg
clasto-Lactacystin-β-lactone	**426102**	Yes	No	A potent and selective proteasome inhibitor. Inhibits the chymotrypsin and trypsin-like peptidase activities of proteasomes. Also inhibits cathepsin A.	100 μg
α-Methylomuralide	**426104**	Yes	No	A cell-permeable α-methyl analog of *clasto*-Lactacystin β Lactone (Omuralide, Cat. No. 426102) that displays improved hydrolytic stability. Reported to be a potent, selective, and irreversible inhibitor of proteasome function (k_{inact} chymotrypsin-like peptidase activity of purified 20S proteasome from bovine brain = 2300 $M^{-1}s^{-1}$ for α-Methylomuralide *vs.* 3060 $M^{-1}s^{-1}$ for Omuralide).	100 μg
MG-115 (Z-LLNva-CHO)	**474780**	Yes	Yes	Potent proteasome inhibitor (IC_{50} = 21 nM and 35 nM for 20S and 26S proteasomes, respectively). Inhibits chymotrypsin-like activity of the proteasomes.	5 mg
MG-132 (Z-LLL-CHO)	**474790**	Yes	Yes	Inhibits chymotrypsin-like activity of the proteasomes (K_i = 4 nM).	1 mg 5 mg
MG-132 in Solution	**474791**	Yes	Yes	A 10 mM solution of MG-132 (Cat. No. 474790) in anhydrous DMSO.	1 mg
NLVS	**482240**	Yes	No	Inhibits chymotrypsin-like, trypsin-like, and peptidylglutamyl-peptidase activities of proteasomes.	500 μg
NP-LLL-VS	**492025**	Yes	No	An intermediate that can be used to prepare radiolabeled ^{125}I-NIP-L$_3$VS for proteasome inhibition studies. NIP-L$_3$VS acts by covalently modifying the active site threonine of the catalytic β-subunit of the proteasome.	500 μg
PR-11	**529643**	Yes	Yes	The active sequence derived from the first 11-amino acids of PR-39 (Cat. No. 529645) that acts as a selective inhibitor of proteasome-mediated IκBα degradation (25% inhibition reported at 500 nM).	1 mg
PR-39, Porcine, Synthetic	**529645**	Yes	Yes	A member of the proline/arginine-rich group of cathelicidin peptides that reversibly binds to the α-7 subunit of 20S proteasome and blocks degradation of NF-κB by the ubiquitin-proteasome pathway without affecting overall proteasome activity.	100 μg
Proteasome Inhibitor I (PSI)	**539160**	Yes	Yes	Inhibits chymotrypsin-like activity of the proteasomes.	1 mg 5 mg
Proteasome Inhibitor II (Z-LLF-CHO)	**539162**	Yes	Yes	Inhibits chymotrypsin-like activity of the proteasomes (K_i = 460 nM).	1 mg 5 mg
Proteasome Inhibitor III [Z-LLL-B(OH)$_2$]	**539163**	Yes	Yes	Inhibits chymotrypsin-like activity of the proteasomes (K_i = 30 pM).	100 μg

Proteasome and Ubiquitination Inhibitors, *continued*

Product	Cat. No.	Cell-permeable?	Reversible?	Comments	Size
Proteasome Inhibitor IV (Z-GPFL-CHO)	**539175**	Yes	Yes	K_is = 1.5 μM for branched chain amino acid preferring, 2.3 μM for small neutral amino acid preferring, and 40.5 μM for chymotrypsin-like activities; IC_{50} = 3.1 μM for PGPH activity. Only weakly inhibits trypsin-like proteasomal activity.	5 mg
NEW Proteasome Inhibitor V	**539177**	Yes	No	A cell-permeable, end-protected norarecoline tripeptide derivative that acts as a potent inhibitor of chymotrypsin-like and trypsin-like proteolytic activities of 20S proteasome (IC_{50} = 520 nM and 2.16 μM, respectively).	5 mg
NEW Proteasome Inhibitor VI	**539178**	Yes	No	A cell-permeable, end-protected tri-leucinyl-norarecoline peptide that acts as a potent and selective inhibitor of chymotrypsin-like activity of 20S proteasome (IC_{50} = 2.33 μM).	5 mg
Ro106-9920	**557550**	Yes	No	A highly selective, irreversible inhibitor of IκBαee ubiquitination (IC_{50} = 2.3 μM). Blocks NF-κB-dependent cytokine expression in human PBMNs (IC_{50}'s ~ 700 nM for TNF-α, IL-1β, and IL-6 inhibition) and rats.	1 mg 5 mg
Ro106-9920, Control	**557551**	Yes	–	A negative control compound for Ro106-9920 (Cat. No. 557550) (IκBαee ubiquitination IC_{50} >80 μM).	1 mg
Tyropeptin A, Synthetic	**657008**	Yes	Yes	IC_{50} = 100 ng/ml for chymotrypsin-like, and 1.5 μg/ml for trypsin-like activities. No effect on PGPH activity even at a concentration of 100 μg/ml.	1 mg 5 mg
Ubiquitin Aldehyde	**662056**	Yes	Yes	Potent and specific inhibitor of multiple ubiquitin hydrolases involved in pathways of intracellular protein modification and turnover.	50 μg
NEW UCH-L1 Inhibitor	**662086**	Yes	Yes	A potent, reversible, competitive, and active site-directed inhibitor of UCH-L1 (K_i = 400 nM; IC_{50} = 880 nM) with ~28-fold greater selectivity over UCH-L3 (Cat. No. 662090).	10 mg
NEW UCH-L3 Inhibitor	**662089**	Yes	No	A selective and potent inhibitor of UCH-L3 (IC_{50} =600 nM) with ~125-fold greater selectivity over UCH-L1 (IC_{50} = 75 μM).	10 mg
YU 101	**688500**	Yes	No	Inhibits chymotrypsin-like activity of the proteasomes. Only weakly inhibits the trypsin-like and peptidylglutamyl peptide hydrolyzing (PGPH) activities of the proteasome.	100 μg

Proteasome Inhibitor Set I

A set of three vials. Each set contains 1 mg of Proteasome Inhibitor I (Cat. No. 539160), 200 mg of Lactacystin (Cat. No. 426100), and 1 mg of MG-132 (Cat. No. 474790).

Cat. No. 539164 **1 Set**

Proteasome Inhibitor Set II

A set of three vials. Each set contains 5 mg of ALLN (Cat. No. 208719), 100 μg each of Epoxomicin (Cat. No. 324800), and clasto-Lactacystin β-Lactone (Cat. No. 426102).

Cat. No. 539165 **1 Set**

Other Inhibitors of Biological Interest

Adenylate Cyclase Inhibitors

Transmembrane receptors of various hormones are coupled to adenylate cyclase (AC) via heterotrimeric G-proteins. Ligand binding to the receptor changes the receptor conformation, allowing it to associate with a G-protein. This results in the activation of the specific G-protein via exchange of GTP for GDP bound to the α-subunit of the G-protein. The activated G-protein in turn activates AC resulting in the conversion of ATP to cAMP. cAMP then acts to regulate a wide variety of cellular processes. AC can couple with both the stimulatory and inhibitory G-proteins (G_s and G_i). Interaction with G_s stimulates its activity and interaction with G_i inhibits its enzymatic activity.

AC is composed of two cytoplasmic domains and two membrane-spanning domains, each of which contains six transmembrane spans. The amino acid sequence of each cytoplasmic domain, which is thought to contain a nucleotide (ATP) binding site, is well conserved among the various subtypes. Although ACs can exist in both particulate and soluble forms, the particulate form is more prevalent in mammals. Based on the conservation of their catalytic domains, three classes of ACs are described: class I-ACs are found in Gram-negative facultative anaerobes, such as *E. coli*; class II-"toxic" ACs, including calmodulin (CaM)-activated ACs are found in pathogenic bacteria, such as *Bordetella pertussis* and *Bacillus anthracis*; and class III-ACs are found in a wide variety of organisms ranging from bacteria to human. Class III-AC also include nine isoforms found in mammals, which are designated AC-1 to AC-9. These nine isoforms are stimulated by the α-subunit of G_s-protein and by forskolin. ACs are also capable of receiving signals from a variety of other sources, such as G_i-α, protein kinase A, C, CaM kinase, and Ca^{2+}/CaM. Hormonal activation of CaM-dependent adenylate cyclase occurs at very low Ca^{2+} levels. The activity of AC is inhibited by high levels of Ca^{2+}, which also activate CaM-dependent phosphodiesterase.

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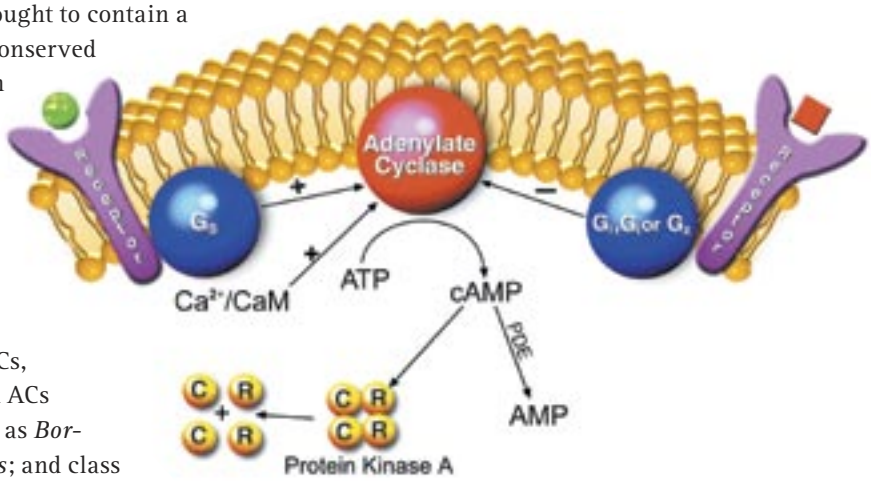

Adenylate Cyclase Inhibitors

Product	Cat. No.	Comments	Size
Adenylyl Cyclase Toxin Inhibitor	**116845**	A cell-permeable inhibitor of adenylate cyclase (IC_{50} = 90 μM).	10 mg
Angiotensin II, Human	**05-23-0101**	An inhibitor of adenylate cyclase activity in spontaneously hypertensive rats.	1 mg 5 mg 25 mg
2′,3′-Diadeoxyadenosine	**288103**	A specific inhibitor of adenylate cyclase (IC_{50} = 9 μM). Also inhibits adenosine deaminase.	5 mg
2′,5′-Dideoxyadenosine	**288104**	A cell-permeable, non-competitive inhibitor of adenylate cyclase (IC_{50} = 3 μM). Binds to the adenosine binding site.	1 mg
MDL-12,330A, Hydrochloride	**444200**	A cell-permeable, irreversible inhibitor of adenylate cyclase (IC_{50} = 250 μM).	1 mg
SQ 22536	**568500**	A cell-permeable adenylate cyclase inhibitor. Blocks PTH-stimulated AC activity (IC_{50} = 200 μM).	5 mg

Angiotensin-Converting Enzyme (ACE) Inhibitors

The renin-angiotensin system plays an important role in electrolyte balance and fluid regulation. Hence, ACE inhibitors have become important clinical tools in the management of hypertension. They block the activation of the renin-aldosterone system, thereby reducing peripheral vascular resistance. ACE inhibitors also improve myocardial oxygen consumption and cardiac output and moderate left ventricular and vascular hypertrophy.

Angiotensin-Converting Enzyme (ACE) Inhibitors

Product	Cat. No.	Comments	Size
Captopril	**211875**	A competitive inhibitor of angiotensin converting enzyme (IC_{50} = 23 - 35 nM).	1 g
Foroxymithine, *Streptomyces nitrosporeus*	**344225**	An inhibitor of Angiotensin I converting enzyme (IC_{50} = 12 μM).	1 mg

ATPase Inhibitors

ATPase Inhibitors

Product	Cat. No.	Comments	Size
Adenosine	**1160**	Exerts a biphasic effect on Ca^{2+}- Mg^{2+}-ATPase activity. Inhibits the activity at ~100 nM levels.	10 g 100 g
Amiloride, Hydrochloride	**129876**	A potent and specific inhibitor of trans-membrane Na^+ entry and Na^+/K^+ ATPase. Diminishes the urinary transepithelial potential difference and short-circuit current (IC_{50} = 300 nM).	100 μg
Atrial Natriuretic Factor 1-28, Rat	**05-23-0301**	Reduces the activity of Na^+-K^+-ATPase in rat kidney and activates neuronal guanylate cyclase.	100 μg
Bafilomycin A1, *Streptomyces griseus*	**196000**	A specific inhibitor of vacuolar-type H^+-ATPase (V-type; K_i = 500 pM) and serves as a valuable tool for distinguishing among different types of ATPases.	10 μg
BHQ	**286888**	Mobilizes Ca^{2+} from the IP_3-sensitive stores by inhibiting microsomal and sarcoplasmic reticulum Ca^{2+}-ATPase activity. Blocks the formation of prostaglandin E2 and prostacyclin (IC_{50} = 0.5 –1.0 μM).	100 mg
(±)-Blebbistatin	**203390**	A cell-permeable, selective, potent, and reversible inhibitor of non-muscle myosin II. Inhibits the ATPase and gliding motility of human platelets (≤100 μM).	5 mg
NEW (-)-Blebbistatin	**203391**	The active enantiomer of (±)-Blebbistatin (Cat. No. 203390) that accounts for the inhibitory activity towards ATPase (IC50 ~2 μM) and myosin II-dependent cellular processes	1 mg
NEW (+)-Blebbistatin	**203392**	The inactive enantiomer of Blebbistatin. Useful as a negative control for the active enantiomer (Cat. No. 203391).	1 mg
BTS	**203895**	A potent inhibitor of Ca^{2+}-stimulated myosin S1 actin-stimulated ATPase activity (IC_{50} = ~5 μM). Also blocks actin-stimulated ATPase activity with similar potency (IC_{50} = 5 μM). Reversibly blocks gliding motility of skeletal muscle myosin ($IC_{50} \leq 2$ μM).	5 mg
Bufalin	**203900**	A cardiotonic steroid that potently inhibits ouabain-sensitive Na^+,K^+-ATPase activity (IC_{50} = 1.4 nM).	10 mg
2,3-Butanedione 2-Monoxime	**203984**	A general reversible inhibitor of myosin ATPases of eukaryotic cells.	500 mg
Calmidazolium Chloride	**208665**	A calmodulin antagonist that also acts as a strong, non-competitive inhibitor of skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase (K_i = 60 nM).	10 mg
Cyclopiazonic Acid, *Penicillium cyclopium*	**239805**	A cell-permeable, reversible inhibitor of endoplasmic reticulum Ca^{2+}-ATPase (IC_{50} = 10 -20 nM).	5 mg
DPC (Diphenylamine-2-carboxylic Acid)	**300265**	A potent non-specific blocker of Cl^- channels that inhibits cystic fibrosis transmembrane regulator ATPase activity.	1 g

Product	Cat. No.	Comments	Size
N-Ethylmaleimide	**34115**	An inhibitor of H^+-ATPase that also suppresses the short-circuit current (IC_{50} = 22 μM) in pancreatic duct cells.	5 g
Folimycin, *Streptomyces* sp.	**344085**	A highly sensitive and specific inhibitor of vacuolar-type H^+-ATPase (V-type; K_i = 20 pM).	10 μg
4-Hydroxynonenal	**393204**	An irreversible inhibitor of Na^+-K^+-ATPase activity (IC_{50} = 120 μM).	1 mg
Hypocrellin B, *Hypocrella bambusae*	**400079**	A lipid-soluble peryloquinone derivative that causes photo-inactivation of Na^+-K^+ -ATPase.	10 mg
Mastoparan	**444898**	Causes a transient Ca^{2+} release from the sarcoplasmic reticulum and inhibits Na^+-K^+-ATPase activity (IC_{50} = 7.5 μM).	1 mg
Mycalolide B, *Mycale* sp.	**475975**	A marine toxin that inhibits actin-activated myosin Mg^{2+}-ATPase activity and also blocks polymerization (IC_{50} = 10 - 50 nM in L1210 leukemia cells).	50 μg
NC-1300-B	**479915**	A long-acting H^+-K^+ ATPase (IC_{50} = 4.4 μM at pH 6.0).	1 mg
Oligomycin	**495455**	An inhibitor of predominantly F1F0-type ATPases (IC_{50} = 50 μM).	10 mg
Omeprazole	**496100**	An inhibitor of Na^+-K^+-ATPase activity (IC_{50} = 186 μM). Acid-degraded omeprazole inhibits Na^+-K^+-ATPase activity with greater potency (IC_{50} = 19 μM).	50 mg
Ouabain, Octahydrate	**4995**	A cardiotonic steroid that acts as an inhibitor of Na^+-K^+-ATPase. Locks the enzyme in an outward facing manner.	1 g 5 g
Phorbol-12,13-dibutyrate	**524390**	Stimulates the phosphorylation of Na^+-K^+ ATPase, thereby inhibiting its activity.	1 mg 5 mg
SCH 28080	**565640**	A selective , reversible inhibitor of H^+-K^+ ATPase (IC_{50} = 2.5 μM).	5 mg
L-Stepholidine, *Stephania intermedica*	**569403**	A dopamine receptor antagonist that inhibits Ca^{2+} ATPase activity (IC_{50} = 31.5 μM).	20 mg
Suramin, Sodium Salt	**574625**	Useful as a reversible and competitive inhibitor of protein tyrosine phosphatases.	50 mg 200 mg
Thapsigargin	**586005**	A cell-permeable tumor-promoting sesquiterpene lactone that releases Ca^{2+} by inhibiting endoplasmic reticular Ca^{2+}-ATPase (IC_{50} = 4 - 13 nM).	1 mg

Inhibitors of Farnesyltransferase (FTase), Geranylgeranyltransferase (GGTase), and Methyltransferase

Prenylation is carried out by cytoplasmic enzymes known as geranylgeranyltransferases and farnesyltransferases that covalently attach 20-carbon (geranylgeranyl) or 15-carbon (farnesyl) isoprenoids to the C-terminus of intracellular proteins via thioether linkages. Protein farnesyltransferase I (FTase I) and protein geranylgeranyltransferase I (GGTase I) recognize a CAAX motif as substrate, where C is cysteine, A represents any aliphatic amino acid, and X is either serine or methionine (FTase I), or leucine (GGTase I). The Rab GGTase II attaches geranylgeranyl groups to proteins that terminate in either CC or CXC motifs.

Many proteins in signal transduction pathways are prenylated. Perhaps the best-characterized farnesylation products are the Ras ATPases. Ras is a guanine nucleotide binding protein that transduces growth and differentiation signals from receptor tyrosine kinases to the nucleus. Mammalian cells express four types of Ras; H-, N-, KA-, and KB-Ras. Mutated or oncogenic forms of Ras require farnesylation for their ability to transform cells. Peptidomimetics designed against the Ras CAAX motif have been shown to reverse oncogenic transformation by H-Ras and inhibit growth of H-Ras-transformed cells. Hence, several types of FTase inhibitors have been designed for use as potential anti-cancer agents. Since Ras proteins are post-translationally modified by FTase and carboxymethylation and they act as a common focal point for signals from growth factor receptors, use of FTase inhibitors is likely to interfere with their action and impede cell proliferation. These inhibitors can be divided into four groups based on the mechanism of their action: (1) competitive inhibitors of farnesyl PPi; (2) peptidomimetic inhibitors based on the CAAX motif; (3) bisubstrate inhibitors; and (4) inhibitors with unknown mechanisms. CAAX peptidomimetics can either function as alternative substrates in the FTase catalyzed reaction, or they can competitively inhibit FTase without serving as substrates.

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Inhibitors of Farnesyltransferase (FTase), Geranylgeranyltransferase (GGTase), and Methyltransferase

Product	Cat. No.	Comments	Size
N-Acetyl-S-farnesyl-L-cysteine (AFC)	**110110**	Exhibits high affinity for S-farnesyl-cysteine methyltransferase (K_m = 20 μM) and thereby inhibits the COOH-terminal methylation of proteins in intact cells as well as in cell-free systems. Also inhibits fMLP-induced superoxide anion generation (IC_{50} = 15 μM).	5 mg
N-Acetyl-S-geranyl-geranyl-L-cysteine (AGGC)	**110115**	Exhibits higher affinity (K_m = 7 μM) than AFC for carboxyl methyltransferase and acts as a more effective inhibitor of fMLP-induced superoxide anion generation (IC_{50} = 4 μM) than AFC.	5 mg
FPT Inhibitor I	**344150**	A highly selective and potent inhibitor of Ras farnesyl-protein transferase (IC_{50} = 83 nM). At much higher concentrations, inhibits geranylgeranyltransferase I (IC_{50} = 26 μM) and II (IC_{50} = 47 μM). Resistant to cleavage by phosphatases.	1 mg
FPT Inhibitor II	**344152**	A highly selective and potent inhibitor of Ras farnesyl-protein transferase (IC_{50} = 75 nM). Also inhibits C15 and C20 protein prenylation in NIH 3T3 cells at higher concentrations. Resistant to cleavage by phosphatases.	1 mg
FPT Inhibitor III	**344154**	A cell-permeable prodrug ester of farnesyl-protein transferase (FPT) inhibitor II that is cleaved to the active FPT inhibitor II by cytosolic esterases. Inhibits Ras processing in cells at about 100 μM concentrations. Inhibits C15 and C20 protein prenylation in NIH 3T3 cells.	1 mg
FTase Inhibitor I	**344510**	A potent, cell-permeable inhibitor of FTase (IC_{50} = 21 nM). Less active against GGTase (IC_{50} = 790 nM).	1 mg
FTase Inhibitor II	**344512**	Potent FTase inhibitor (IC_{50} = 50 nM).	1 mg
FTase Inhibitor III	**344514**	Most potent synthetic inhibitor of $p21^{ras}$ FTase (IC_{50} = 12 nM for rat brain FTase).	1 mg
FTI-276	**344550**	A highly potent and selective inhibitor of FTase *in vitro* (IC_{50} = 500 pM). Less active against GGTase (IC_{50} = 50 nM).	250 μg
FTI-277	**344555**	A cell-permeable form of FTI-276 (Cat. No. 344550). Inhibits H-Ras processing in whole cells (IC_{50} = 100 nM).	250 μg

Product	Cat. No.	Comments	Size
GGTI-286	**345878**	A cell-permeable form of GGTI-287 (Cat. No. 345880); a very potent inhibitor of the processing of the geranylgeranylated Rap1A protein (IC_{50} = 2 μM).	250 μg
GGTI-287	**345880**	A highly potent and selective GGTase inhibitor *in vitro* (IC_{50} = 5 nM). Inhibits FTase only at higher concentrations (IC_{50} = 25 nM).	250 μg
GGTI-297	**345882**	A potent and selective GGTase I Inhibitor (IC_{50} = 50 nM) relative to FTase (IC_{50} = 200 nM).	250 μg
GGTI-298	**345883**	A cell-permeable prodrug form of GGTase I inhibitor, GGTI-297 (Cat. No. 345882). Inhibits the processing of Rap1A (IC_{50} = 3 μM) but has no effect on the processing of H-Ras even at higher concentrations (15 μM).	250 μg
GGTI-2133	**345884**	A potent and selective non-thiol inhibitor of GGTase I (IC_{50} = 38 nM) with a 140-fold selectivity over FTase (IC_{50} = 5.4 μM).	250 μg
GGTI-2147	**345885**	The methyl ester derivative of GGTI-2133 (Cat No. 345884). Selectively inhibits GGTase I over FTase in whole cells. Blocks the geranylgeranylation of Rap1A with an IC_{50} value over 60-fold lower than that required to disrupt the farnesylation of H-Ras (IC_{50} = 500 nM for Rap1A versus IC_{50} > 30 μM for H-Ras).	250 μg
Gliotoxin, *Gladiocladium fimbriatum*	**371715**	This fungal epipolydithioketopiperazine toxin is a modest (IC_{50} = 1.1 μM) inhibitor of FTase.	1 mg
α-Hydroxyfarnesylphosphonic Acid	**390601**	A potent and selective competitive inhibitor of farnesyl-protein transferase (IC_{50} = 30 nM). At higher concentrations, it inhibits GGTase I (IC_{50} = 35.8 μM) and II (IC_{50} = 67 μM). Useful for inhibition of Ras processing *in vivo* and *in vitro*.	1 mg
L-744,832	**422720**	A potent and selective thiol-containing peptidomimetic farnesyltransferase (FTase) inhibitor with anti-tumor activities. Rapidly blocks p70s6k activation and DNA synthesis, and promotes apoptosis in transgenic mice, induces p21 expression and arrests cells in G_1 phase.	5 mg
Manumycin A, *Streptomyces parvulus*	**444170**	A potent and selective inhibitor of FTase (IC_{50} = 5 μM) compared to GGTase (IC_{50} = 180 μM).	1 mg

Inhibitors of Glycoprotein Processing and Trafficking

N- and O-glycan structures contribute significantly to biological recognition and cell adhesion during immune surveillance, inflammatory reactions, hormone action, and viral infections. The cell- and tissue-specific changes in cell surface oligosaccharides during various phases of development indicate that these structures are also involved in cell adhesion and migration during embryogenesis. Modifications in the branching and extension of N-glycans are also observed on cells undergoing oncogenic transformation. These modifications may result in alterations in cell adhesion and contribute to the invasiveness and metastatic potential of malignant cells.

Inhibitors of glycoprotein processing act late in the N-glycan processing pathway and block the oncogene-induced changes in cell surface oligosaccharide structures. The various processing inhibitors provide useful tools to understand the role of specific kinds of oligosaccharide structures in the function of various glycoproteins. Because of the specificity of the processing inhibitors for individual glycosidases, these compounds are also valuable reagents to differentiate various enzymatic activities in the cells.

Inhibitors of Glycoprotein Processing and Trafficking

Product	Cat. No.	Comments	Size
p-Aminophenyl-β-D-thiogalactopyranoside	**164604**	Inhibitor of *E. coli* β-galactosidase. Can be conjugated to agarose and used in protein purification.	250 mg 1 g
Australine, Hydrochloride, *Castanospermum australe*	**189422**	Pyrrolizidine alkaloid that inhibits α-glucosidase, amyloglucosidase, and glucosidase I. Inhibits glycoprotein processing at the glucosidase I step, resulting in the accumulation of glycoproteins containing $Glc_3Man_{79}(GlcNAc)2$-oligosaccharides. Does not inhibit α- or β-galactosidase, β-glucosidase, or α- or-mannosidase.	1 mg
epi-Australine, Hydrochloride, *Castanospermum australe*	**189423**	Epimer of the pyrrolizidine alkaloid Australine (Cat. No. 189422). Does not inhibit glucosidase I or II, but does inhibit α- and β-mannosidase. Useful as a negative control for inhibition studies with Australine (Cat. No. 189422).	500 µg
Benzyl-2-acetamido-2-deoxy-α-D-galactopyranoside	**200100**	Used as an inhibitor of O-linked glycosylation in a variety of cell lines. It has also been used to inhibit 2,3(O)-sialyltransferase and disrupt glycoprotein targeting in HT-29 cells. Substrate for N-acetyl-β-D-glucosaminyltransferase.	100 mg
N-(*n*-Butyl)deoxygalactonojirimycin	**203994**	A potent and selective inhibitor of α-D-galactosidase.	5 mg
N-Butyldeoxynojirimycin, Hydrochloride	**203996**	A non-hormonal, alkylated iminosugar that acts as a transition state analog inhibitor of ceramide-specific glycosyltransferases and ER α-glucosidases I and II. Displays a broad-spectrum anti-viral activity by aiding the misfolding of glycoproteins.	10 mg
2-Deoxy-D-galactose	**259580**	Suggested to act as an inhibitor of fucosylation. It has also been used for competitive elution of Anadarin P lectin (a galactosyl-binding lectin from blood clam).	1 g
Deoxyfuconojirimycin, Hydrochloride	**259541**	Potent and specific competitive inhibitor (K_i = 10 nM) of human liver α-fucosidase.	5 mg
Deoxygalactonojirimycin, Hydrochloride	**259544**	A potent and selective α-galactosidase inhibitor.	5 mg
1-Deoxymannojirimycin, Hydrochloride	**260575**	Special α-mannosidase I inhibitor that blocks conversion of high mannose to complex oligosaccharides.	5 mg
1-Deoxynojirimycin, Hydrochloride	**260684**	Specific glucosidase inhibitor, including trimming glucosidases I and II, that sequentially removes the three glucose residues from precursor $Glc_3Man_9GlcNAc_2$ in N-linked glycan biosynthesis.	1 mg 10 mg
Deoxynojirimycin, N-Methyl-	**457228**	An inhibitor of glucosidase I (but not glucosidase II) that interfers with the normal processing of asparagine-linked glycoproteins.	5 mg
Kifunensine, *Kitasatosporia kifunense*	**422500**	A potent alkaloid inhibitor of mannosidase I. An ineffective inhibitor of mannosidase II and the endoplasmic reticulum α-mannosidase.	1 mg

Inhibitors of Glycoprotein Processing and Trafficking, *continued*

Product	Cat. No.	Comments	Size
Mannostatin A, Hydrochloride	**444042**	A potent glycosidase inhibitor that blocks mannosidase II processing in the Golgi more effectively than Swainsonine (Cat. No. 574775).	1 mg
Nikkomycin Z, *Streptomyces tendae*	**481995**	Antibiotic that inhibits the biosynthesis of chitin in the cell wall by competitively inhibiting chitin synthase. Exhibits structural similarity to UDP-N-acetylglucosamine.	5 mg
DL-*threo*-PDMP, Hydrochloride	**513100**	PDMP closely resembles the natural sphingolipid substrate of brain glucosyltransferase and is a potent and competitive inhibitor of this enzyme.	50 mg
Swainsonine, *Swainsona canescens*	**574775**	Reversible active-site inhibitor of lysosomal α-mannosidase. Blocks the processing of high mannose to complex type oligosaccharides.	500 µg
Tunicamycin, *Streptomyces lysosuperficus*	**654380**	A nucleoside antibiotic that inhibits N-linked glycosylation and blocks the formation of N-glycosidic protein-carbohydrate linkages.	10 mg 50 mg

NF-κB Activation Inhibitors

NF-κB, a eukaryotic transcription factor, consists of homo- or heterodimers of different subunits, which belong to a family of Rel/NF-κB proteins. Five different Rel proteins [p50, p52, p65 (Rel A), RelB, and c-Rel] have been identified thus far. The most prevalent activated form of NF-κB is a heterodimer of p50 or p52 subunit and p65, which contains transactivation domains necessary for gene induction. In unstimulated cells, NF-κB is sequestered in the cytoplasm in an inactive form, bound to regulatory proteins called inhibitors of κB (IκB), of which IκBα and IκBβ are considered to be the most important. IκBα is associated with transient NF-κB activation, whereas IκBβ is involved in sustained activation.

The activity of NF-κB is tightly regulated by interaction with inhibitory IκB proteins. In most resting cells, NF-κB is sequestered in the cytoplasm in an inactive form associated with inhibitory molecules, such as IκBα, IκBβ, IκBε, p105, and p100. This interaction blocks the ability of NF-κB to bind to DNA and results in the NF-κB complex being primarily localized to the cytoplasm due to a strong nuclear export signal in IκBα.

Stimulation of cells by inflammatory cytokines, UV light, or reactive oxygen species leads to the rapid phosphorylation, ubiquitination, and ultimately proteolytic degradation of IκB, which frees NF-κB from the NF-κB-IκB complex. NF-κB then translocates to the nucleus where it binds to κB enhancer elements of pro-inflammatory target genes to induce transcription. NF-κB is highly activated at sites of inflammation in diverse diseases and induces transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, MMPs, COX-2, and inducible nitric oxide (iNOS). Hence, NF-κB has been considered as a desirable target for therapy in various inflammatory diseases.

In most cancer cells, NF-κB is constitutively active and resides in the nucleus. In some cases, this may be due to chronic stimulation of the IKK pathway, while in others the gene encoding IκBα may be defective. Such continuous nuclear NF-κB activity not only protects cancer cells from apoptotic cell death, but may even enhance their growth activity. Designing anti-tumor agents to block NF-κB activity or to increase sensitivity to conventional chemotherapy may have great therapeutic value.

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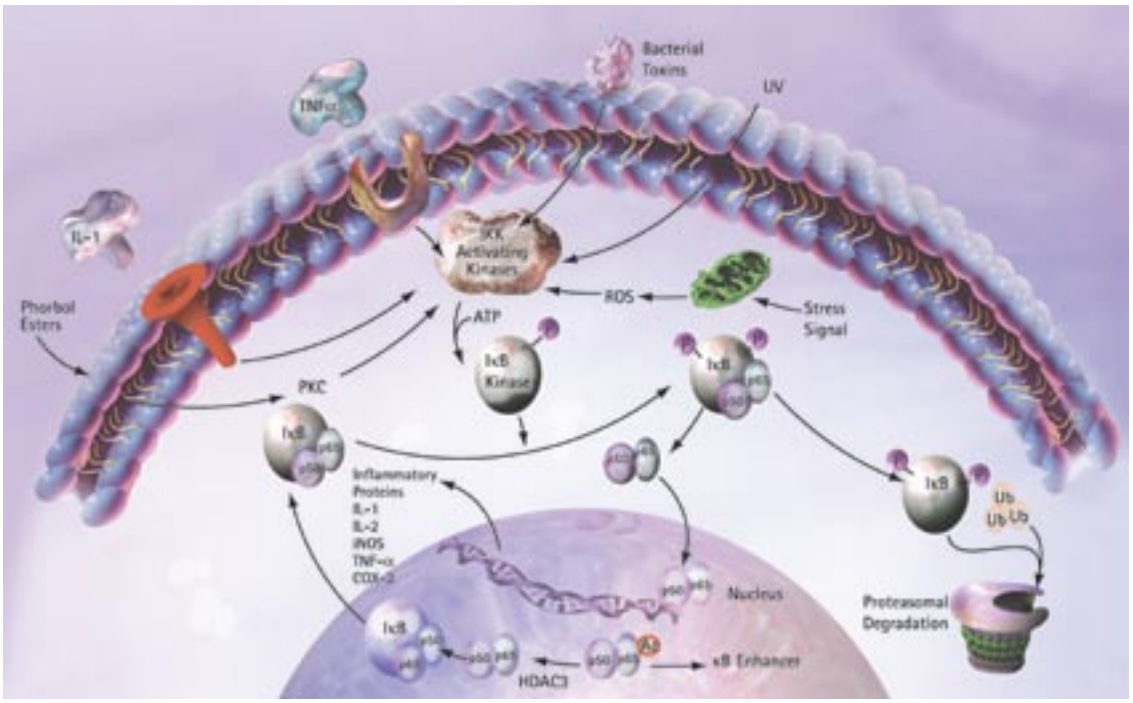

NF-κB Activation Inhibitors

Product	Cat. No.	Comments	Size
BAY 11-7082	**196870**	Potential anti-inflammatory agent. Selectively and irreversibly inhibits the TNFα-inducible phosphorylation of IκBα (IC_{50} = 10 μM) without affecting the constitutive IκBα phosphorylation. Decreases nuclear translocation of NF-κB and inhibits TNFα-induced surface expression of the endothelial-leukocyte cell adhesion molecules E-selectin, VCAM-1, and ICAM-1.	10 mg
BAY 11-7085	**196872**	Exhibits biological properties similar to that of BAY 11-7082 (Cat. No. 196870). BAY 11-7085 has also been shown to have potent anti-inflammatory properties *in vivo*.	10 mg
CAPE	**211200**	An active component of propolis from honeybee hives with antiviral, anti-inflammatory, and immunomodulatory properties. Has been shown to act as a potent and specific inhibitor of NF-κB activation.	25 mg
(E)-Capsaicin	**211274**	An active constituent of cayenne pepper that has anti-nociceptive and anti-inflammatory effects. Inhibits NF-κB activation by TNF.	100 mg
Gliotoxin, *Gladiocladium fimbriatum*	**371715**	An immunosuppressive secondary metabolite produced by several pathogenic fungi that specifically inhibits NF-κB activation in B and T cells at nanomolar concentrations.	1 mg
Helenalin, A. *chamissonis* ssp. *foliosa*	**374000**	A cell-permeable pseudoguainolide sesquiterpenoid lactone that inhibits NF-κB-DNA binding activity by selectively alkylating the p65 subunit of NF-κB. Does not inhibit IκB degradation or NF-κB nuclear translocation.	500 μg
Hypoestoxide, *Hypoestes rosea*	**401006**	A naturally occurring, cell-permeable diterpene with anti-inflammatory properties. Acts as a selective and direct inhibitor of IκB kinase (IC_{50} = 24 μM) in TNF-α stimulated HeLa cells thereby prevents NF-κB activation.	1 mg
IκB Kinase Inhibitor Peptide, Cell-Permeable	**401477**	A 14-amino acid peptide corresponding to the active IκB phosphorylation recognition sequence, linked to the hydrophobic region of the fibroblast growth factor signal peptide to aid in cellular delivery. Specifically inhibits LPS-induced IκB degradation by IκB kinases (IKK) in RAW 264.7 cells (< 50 μg/ml) and prevents NF-κB activation.	1 mg
IκB Kinase Inactive Control peptide, Cell-permeable	**401478**	An inactive control for IκB Kinase Inhibitor Peptide (Cat. No. 401477). Corresponds to the mutated recognition sequence of IκB (Ser^{32} → Ala and Ser^{36} → Ala), linked to the hydrophobic region of the fibroblast growth factor signal peptide to aid in cellular delivery. Does not have any inhibitory effect on LPS-induced IκB degradation by IκB kinases (IKK) in RAW 264.7 cells at 50 μg/ml.	1 mg
NEW IKK Inhibitor II, Wedelolactone	**401474**	The naturally isolated active ingredient of the herbal medicine, *Eclipta alba*, that acts as a selective and irreversible inhibitor of IKKα and β kinase activity (IC_{50} <10 μM). Inhibits NF-κB-mediated gene transcription in cells by blocking the phosphorylation and degradation of IκB.	1 mg
NEW IKK Inhibitor III, BMS-345541	**401480**	A cell-permeable, potent, selective, and allosteric site-binding inhibitor of IKK-2 (IC_{50}~ 300 nM). Exhibits ~10 fold greater selectivity over IKK-1 (IC_{50} ~4 μM).	1 mg
NEW IKK-2 Inhibitor, SC-514	**401479**	A cell-permeable, potent, reversible, ATP-competitive, and highly selective inhibitor of IKK-2 (IC_{50} ~3 - 12 μM for IKK-2 homodimer, IKK-1/IKK-2 heterodimer, and IKK-2). Shown to specifically block NF-κB-dependent gene expression, but not MAP kinase pathways, in stimulated RASF synovial fibroblast cells. Does not inhibit the phosphorylation and activation of the IKK complex.	1 mg
NEW IKK-2 Inhibitor IV	**401481**	A cell-permeable, potent, and selective inhibitor of IKK-2 (IC_{50} = 18 nM) with selectivity over IKK-1, JNK, and p38 MAPK.	500 μg
Isohelenin, *Inula* sp.	**416157**	A cell-permeable sesquiterpene lactone with anti-inflammatory properties. Acts as a highly specific, potent, and irreversible inhibitor of NF-κB activation by preventing IκBα degradation. Does not affect the DNA binding activity of activated NF-κB or inhibit Fyn and Src kinase activities.	1 mg
Kamebakaurin, *Isodon japonicus*	**420340**	A potent, irreversible inhibitor of NF-κB activation (100% inhibition at ~26.6 μM) that acts by directly targeting the DNA-binding activity of p50 and blocking the expression of anti-apoptotic NF-κB target genes. Does not affect the induced degradation of IκB-α and nuclear translocation of NF-κB.	500 μg

NF-κB Activation Inhibitors, *continued*

Product	Cat. No.	Comments	Size
NEMO-Binding Domain Binding Peptide, Cell-Permeable	**480025**	A cell-permeable antennapedia-NBD (NEMO binding domain) (wild type) fusion peptide that exhibits anti-inflammatory activity in mouse model of acute inflammation. NBD is an amino-terminal α-helical region of the NEMO (NF-κB essential modifier; IKKγ) associated with a carboxyl-terminal segment of IKKα and IKKβ. Blocks the association of NEMO with the IKK complex and prevents NF-κB activation.	500 µg
NEMO-Binding Domain Binding Peptide, Cell-permeable, Negative Control	**480030**	A cell-permeable, antennapedia-NBD mutated (Trp^{739} → Ala and Trp^{741}→ Ala) fusion peptide analog of NEMO-Binding Domain Binding peptide (Cat. No. 480025) that serves as a negative control. Reported to be defective in binding to NEMO.	500 µg
NEW NF-κB Activation Inhibitor	**481406**	A cell-permeable quinazoline compound that acts as a potent inhibitor of NF-κB transcriptional activation (IC_{50} = 11 nM in Jurkat cells) and LPS-induced TNF-α production (IC_{50} = 7 nM in murine splenocytes). Does not exhibit cellular toxicity at concentrations required for inhibition of NF-κB transcriptional activation (IC_{50} >10 µM) or TNF-α production (IC_{50} >10 µM).	1 mg
NF-κB SN50, Cell-Permeable Inhibitor Peptide	**481480**	Contains the nuclear localization sequence (NLS) of the transcription factor NF-κB p50 linked to the hydrophobic region (h-region) of the signal peptide of Kaposi fibroblast growth factor (K-FGF). The peptide N-terminal K-FGF h-region confers cell-permeability, while the NLS (360-369) inhibits translocation of the NF-κB active complex into the nucleus.	500 µg
NF-κB SN50M, Cell-Permeable Inactive Control Peptide	**481486**	An inactive control for SN50 peptide (Cat. No. 481480). Corresponds to the SN50 peptide sequence with substitutions of Lys^{363} for Asn and Arg^{364} for Gly in the NLS region.	500 µg
Parthenolide, *Tanacetum parthenium*	**512732**	A sesquiterpene lactone with anti-inflammatory, antisecretory, and spasmolytic properties. Inhibits NF-κB and activation of MAP kinase.	50 mg
PPM-18	**529570**	A novel, cell-permeable, anti-inflammatory agent that inhibits the expression of inducible nitric oxide synthase (iNOS; IC_{50} ~5 µM). Acts by blocking the activation of NF-κB *in vitro* and *in vivo*.	10 mg
Sulfasalazine	**573500**	An anti-inflammatory agent that acts an inhibitor of glutathione S-transferase (IC_{50} = 10 µM in H-69 cell line). Prevents NF-κB activation and induces apoptosis in T lymphocytes.	100 mg
TIRAP Inhibitor Peptide, Cell-Permeable	**613570**	A synthetic, cell-permeable peptide corresponding to mouse toll-interleukin 1 receptor (TIR) domain-containing adapter protein 138 - 151 (TIRAP) fused to the *Drosophila* Antennapedia sequence. Specifically inhibits LPS-induced, but not CpG-induced, NF-κB activation, PKR phosphorylation, and JNK phosphorylation in RAW.κB cells at ~ 40 µM. Also reported to block IκBα degradation.	1 mg
TIRAP Inhibitor Peptide, Control, Cell-Permeable	**613571**	A cell-permeable synthetic peptide containing mouse toll-interleukin 1 receptor (TIR) domain-containing adapter protein 151 - 138 reverse sequence (TIRAP) fused to the *Drosophila* Antennapedia sequence. Serves as a control for TIRAP Inhibitor Peptide (Cat. No. 613570).	1 mg

Phosphodiesterase (PDE) Inhibitors

cAMP and cGMP, two important second messenger molecules, are hydrolyzed by phosphodiesterases (PDEs) in the cell, leading to cessation of cAMP- or cGMP-dependent effects. At least nine major classes of PDEs have been reported that differ in their kinetic properties. Many of these isozymes are differentially expressed and regulated in different cells and exhibit distinct selectivity for cAMP or cGMP. However, these isozymes exhibit significant sequence homology in their catalytic domain. Due to their involvement in inflammation, asthma, and cardiovascular complication, PDEs are considered to be attractive targets for pharmacological intervention. A number of PDE inhibitors have been developed that target specific isozymes, thereby increasing tissue selectivity and minimizing side effects.

Table 5 Classification of Phosphodiesterases

PDE	Regulatory Mechanisms	Substrate
I	CaM-dependent	cAMP cGMP
II	c-GMP-stimulated	cAMP cGMP
III	cGMP-inhibited	cAMP
IV	cAMP-specific	cAMP
V	cGMP-specific	cGMP
VI	Photoreceptor cGMP-specific	cGMP
VII	cAMP-specific rolipram-insensitive	cAMP
VIII	cAMP-specific IBMX-insensitive	cAMP
IX	cGMP-specific	cGMP

Phosphodiesterase Inhibitors

Product	Cat. No.	Comments	Size
Calmidazolium Chloride	**208665**	An analog of sepazonium that is at least 150 times more potent than Trifluoperazine (Cat. No. 642150) as an inhibitor of brain PDE I (IC_{50} = 10 nM).	10 mg
Chlorpromazine, Hydrochloride	**215921**	An inhibitor of PDE I (IC_{50} = 17 μM).	500 mg
Cilostamide	**231085**	A selective inhibitor of PDE III (IC_{50} = 70 nM).	10 mg
Denbufylline	**253500**	A xanthine derivative that acts as a selective inhibitor of phosphodiesterase IV (PDE IV; K_i ~1 μM).	5 mg
Dipyridamole	**322328**	A selective inhibitor of PDE V (IC_{50} = 900 nM).	100 mg
EHNA, Hydrochloride	**324630**	A potent inhibitor of PDE II (IC_{50} = 800 nM). Does not inhibit other PDE isozymes (IC_{50} >100 μM).	10 mg
EMD 41000, Dihydrochloride	**324663**	Acts as a more potent inhibitor of PDE III (IC_{50} = 13 μM) than its oxidized analog Isomazole (Cat. No. 419545).	10 mg
Etazolate, Hydrochloride	**331500**	A selective inhibitor of PDE IV (IC_{50} = 2 μM).	5 mg
3-Isobutyl-1-methylxanthine	**410957**	A non-specific inhibitor of cAMP and cGMP phosphodiesterases (IC_{50} = 2-50 μM).	250 mg 1 g
Isomazole, Dihydrochloride	**419545**	A cardiotonic agent that is shown to inhibit PDE III and PDE V compared to PDE IV (IC_{50} = 42 μM for guinea pig PDE III; 58 μM for porcine PDE V; >100 μM for guinea pig PDE IV).	10 mg
8-Methoxymethyl-3-isobutyl-1-methylxanthine	**454202**	A selective inhibitor of PDE I (IC_{50} = 4 μM).	10 mg
4-{[3′,4′-(Methylene-dioxy)benzyl]amino}-6-methoxy-quinazoline	**475250**	A potent and specific inhibitor of PDE V (IC_{50} = 230 nM).	1 mg
Milrinone	**475840**	A selective inhibitor of PDE III (IC_{50} = 300 nM).	10 mg
MY-5445	**474925**	A selective inhibitor of PDE V (IC_{50} = 600 nM).	10 mg
NEW Phosphodiesterase V Inhibitor II	**524714**	A cell-permeable, potent, and highly selective phosphodiesterase V inhibitor (IC_{50} = 5 nM for bovine aorta PDE V; IC_{50} >10 μM for human recombinant PDE I & III, and for bovine aorta PDE II & IV).	5 mg
Phosphodiesterase V Inhibitor, T-0156	**524716**	A cell-permeable, highly potent, selective, competitive inhibitor of phosphodiesterase type V isozyme (IC_{50} = 230 pM). Inhibits other PDE isozymes at much higher concentrations (56 nM, 63 μM, >100 μM for PDE V, PDE VI, PDE IV, and PDE I-III, respectively).	5 mg 25 mg

Phosphodiesterase Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Ro-20-1724	**557502**	A selective inhibitor of PDE IV (IC_{50} = 2 μM).	100 mg
Rolipram	**557330**	A selective competitive inhibitor of PDE IV (IC_{50} = 800 nM). Does not inhibit PDE I or PDE II, even at 100 μM. Only a weak inhibitor of PDE III (IC_{50} = 100 μM). A rolipram-insensitive PDE IV subtype is also known to exist.	5 mg
Trequinsin, Hydrochloride	**382425**	An extremely potent inhibitor of PDE III (IC_{50} = 300 pM) and platelet aggregation *in vitro*.	10 mg
Vinpocetine	**677500**	A selective inhibitor of PDE I (IC_{50} = 20 μM).	20 mg
W-5, Hydrochloride	**681625**	A calmodulin antagonist that inhibits PDE I (IC_{50} = 240 μM).	1 mg
W-7, Hydrochloride	**681629**	A calmodulin antagonist that inhibits PDE I (IC_{50} = 28 μM)	10 mg
W-7, Immobilized	**681630**	An immobilized form of the calmodulin antagonist (Cat. No. 681629) that is covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. Useful to affinity-precipitate calmodulin and other functionally related proteins from cell or tissue extracts. 1 set = 25 mg of W-7 Immobilized beads and 25 mg of control beads.	1 set
W-12, Hydrochloride	**681635**	A calmodulin antagonist that inhibits PDE I (IC_{50} = 260 μM).	1 mg
W-13, Hydrochloride	**681636**	A calmodulin antagonist that inhibits PDE I (IC_{50} = 68 μM).	1 mg
Zaprinast	**684500**	A selective inhibitor of PDE V (IC_{50} = 450 nM).	25 mg

Phosphodiesterase Inhibitor Set I

Provided as a set of 4 vials. Each set contains 10 mg of 8-Methoxymethyl-3-isobutyl-1-methylxanthine (Cat. No. 454202), a Ca^{2+}/CaM-dependent PDE (PDE I) inhibitor; 1 mg of 4-{[3,4 -(Methylenedioxy)benzyl]amino}-6-methoxy-quinazoline (Cat. No. 475250), a cGMP-specific PDE (PDE V) inhibitor; 5 mg of Rolipram (Cat. No. 557330), a cAMP-specific PDE (PDE IV) inhibitor; and 10 mg of Trequinsin, Hydrochloride (Cat. No. 382425), a cGMP-inhibited PDE (PDE III) inhibitor.

Cat. No. 524718 **1 set**

Phosphodiesterase Inhibitor Set II

Provided as a set of 5 vials. Each set contains 100 mg of Ro-20-1724 (Cat. No. 557502), 25 mg of Zaprinast (Cat. No. 684500), 10 mg each of EHNA, Hydrochloride (Cat. No. 324630), 8-Methoxymethyl-3-isobutyryl-1-methylxanthine (Cat. No. 454202), and Quazinone (Cat. No. 551490).

Cat. No. 524719 **1 set**

Plasminogen Activator Inhibitors

Tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) and their inhibitor, plasminogen activator inhibitor 1 (PAI-1) are involved in the regulation of tissue morphogenesis and differentiation. Plasminogen activator-mediated extracellular matrix degradation plays an important role in the development of tumors and tumor metastasis. Over-expressed tPA and uPA systems are reported in patients with aggressive metastasizing tumors. Hence, inhibition of plasminogen activation is an important pharmacological target for blocking metastasis and reducing primary tumor growth.

tPA is a serine protease that converts plasminogen to plasmin and can trigger the degradation of extracellular matrix proteins. The tPA/plasmin proteolytic system has been implicated in both physiological and pathological processes. In the brain tPA promotes events associated with synaptic plasticity such as motor learning and long-term potentiation. Under non-inflammatory conditions it also contributes to excitotoxic neuronal death. Outside the nervous system tPA is mainly found in the blood, where it functions as a thrombolytic enzyme and prevents excess fibrin accumulation in vessels.

PAI-1, a serine proteinase inhibitor, is a 50 kDa glycoprotein that acts as an important physiological inhibitor of tPA and uPA. It plays a crucial role in the regulation of vascular thrombosis, tumor invasion, neovascularization, and inflammation. Higher plasma levels of PAI-1 are correlated with an increased risk for cardiovascular diseases.

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Plasminogen Activator Inhibitors

Product	Cat. No.	Comments	Size
Amiloride, Hydrochloride	**129876**	A competitive inhibitor of uPA activity (K_i = 7 μM).	100 mg
Plasminogen Activator Inhibitor-1, Human, Recombinant	**528205**	Primary inhibitor of both tPA and uPA. PAI-1 is synthesized by vascular epithelium and hepatocytes. Used as a marker for acute myocardial infarction and in the diagnosis of several thrombolytic disorders. Elevated levels are found in subjects with accelerated coronary artery disease. May serve as an independent and strong prognostic factor in breast cancer patients. Patients having elevated levels of PAI-1 in their primary tumors are more prone to relapse.	50 μg
Plasminogen Activator Inhibitor-1, Elastase Specific, Human, Recombinant, *E. coli*	**528209**	PAI-1 with a point mutation at amino acid 346 from arginine to alanine. This mutation results in an alteration of the target specificity of PAI-1 from the plasminogen activators tPA and uPA to elastase. PAI-1 is normally a substrate for pancreatic and neutrophil elastase. However, this mutation results in an inhibitor as potent as antitrypsin.	50 μg
Plasminogen Activator Inhibitor-1, Mutant, Human, Recombinant	**528208**	Highly purified preparation of an altered form of human PAI-1 containing four mutated amino acids. Mutant PAI-1 is virtually unable to go latent and is stable at elevated temperature and pH for extended periods of time ($t_{1/2}$ = 145 hours at 37˚C, pH 7.4). Inhibits uPA (K_i = 5.1 x 10^6 $M^{-1}sec^{-1}$) and tPA (K_i = 7.9 x 10^5 $M^{-1}sec^{-1}$).	50 μg
Plasminogen Activator Inhibitor-1, Mutant, Mouse, Recombinant	**528213**	This inhibitor contains a single minor conservative amino acid substitution Ile^{91}→Leu^{91} that gives the inhibitor increased half life (about 4-fold increase over the native recombinant form). Stable when stored at or below pH 6.6. Has good stability with $t_{1/2}$ = 8 to 9 hours at 25˚C, pH 7.4.	50 μg
Plasminogen Activator Inhibitor-1, Rat, Recombinant	**528214**	Inhibits human uPA (K_i = 6.3 x 10^6 $M^{-1}sec^{-1}$). Stable when stored at or below pH 6.6.	50 μg

Protein Synthesis Inhibitors

Many inhibitors used to block protein synthesis are either antibiotics or toxins. Their mechanism of action includes the interruption of peptide-chain elongation, blocking the A site of ribosomes, and misreading of the genetic code. Some of them may also prevent the attachment of oligosaccharide side chains to glycoproteins.

Protein Synthesis Inhibitors

Product	Cat. No.	Comments	Size
Anisomycin, *Streptomyces griseolus*	**176880**	A reversible inhibitor of protein synthesis at the translation step.	10 mg
Blasticidin S, Hydrochloride, *Streptomyces griseochromogenes*	**203350**	Nucleoside antibiotic that specifically inhibits protein synthesis in both prokaryotes and eukaryotes.	25 mg
Chloramphenicol	**220551**	Inhibits protein synthesis by binding to the 50S ribosomal subunit and blocking the formation of the peptide bond by inhibiting peptidyl transferase activity. It is a potent inhibitor of mitochondrial protein synthesis in eukaryotic cells.	25 g 100 g 500 g
Cycloheximide	**239763**	An antifungal antibiotic that inhibits protein synthesis in eukaryotes but not in prokaryotes. Interacts directly with the translocase enzyme, interfering with the translocation step. Inhibits cell-free protein synthesis in eukaryotes.	1 g 5 g
Cycloheximide, High Purity	**239764**	An antifungal antibiotic that inhibits protein synthesis in eukaryotes but not in prokaryotes. Interacts directly with the translocase enzyme, interfering with the translocation step. Inhibits cell-free protein synthesis in eukaryotes.	100 mg 1 g
Cycloheximide in Solution	**239765**	A 100 mg/ml DMSO solution of cycloheximide (Cat. No. 239763) in DMSO.	1 ml
Emetine, Dihydrochloride	**324693**	An irreversible inhibitor of protein synthesis in eukaryotes. Blocks the movement of ribosomes along the mRNA.	250 mg
Erythromycin, *Streptomyces erythreus*	**329815**	Inhibits bacterial protein synthesis by binding to 70S ribosomes and stimulating the dissociation of peptidyl-tRNA from ribosomes. Inhibits elongation of the protein by peptidyltransferase that forms peptide bonds between the amino acids, by preventing the ribosome from translocating down the mRNA.	5 g 25 g
G418 Sulfate, Cell-Culture Tested	**345810**	An aminoglycoside antibiotic related to gentamycin that irreversibly binds to ribosomes and inhibits protein synthesis in prokaryotic and eukaryotes.	250 mg 500 mg 1 g 5 g 25 g
G418 Sulfate, Sterile-Filtered Aqueous Solution Cell-Culture Tested	**345812**	An aminoglycoside antibiotic related to gentamycin that irreversibly binds to ribosomes and inhibits protein synthesis in prokaryotic and eukaryotes.	10 ml 20 ml 50 ml
Hygromycin B	**400051**	An aminoglycoside antibiotic that blocks protein synthesis in prokaryotes and eukaryotes.	100 KU 1 MU 5 MU 10 MU
Kanamycin Sulfate, *Streptomyces kanamyceticus*	**420311**	An inhibitor of protein biosynthesis that acts on the 70S ribosome, causing misreading of the genetic code.	5 g 25 g
Kanamycin Sulfate, *Streptomyces kanamyceticus*, Cell Culture-Tested	**420411**	An inhibitor of protein biosynthesis that acts on the 70S ribosome, causing misreading of the genetic code.	5 g 25 g
Nigrin b, *Sambucus nigra* L.	**481991**	A novel two-chain type 2 ribosome-inactivating protein isolated from elderberry bark of *Sambucus nigra* L. that inhibits protein synthesis by inactivation of mammalian ribosomes.	1 mg
NEW Nourseothricin, *S. noursei*	**450150**	An amino-glycoside antibiotic that interferes with protein synthesis by inducing misreading in translation.	100 mg 500 mg
Puromycin, Dihydrochloride	**540222**	An aminonucleoside antibiotic that acts as a prokaryotic and eukaryotic protein synthesis inhibitor. Resembles the aminoacyl-adenylyl terminus of aminoacyl-tRNA and competes for binding to the "A site" of the large ribosomal subunit.	25 mg 100 mg
Puromycin, Dihydrochloride, Cell Culture-Tested	**540411**	An aminonucleoside antibiotic that acts as a prokaryotic and eukaryotic protein synthesis inhibitor. Resembles the aminoacyl-adenylyl terminus of aminoacyl-tRNA and competes for binding to the "A site" of the large ribosomal subunit.	25 mg 100 mg
Spectinomycin, Dihydrochloride, Pentahydrate, *Streptomyces* sp.	**567570**	Inhibits protein synthesis by binding to the 30S ribosomal subunit to prevent the formation of an initiation complex with messenger RNA.	10 g

Protein Synthesis Inhibitors, *continued*

Product	Cat. No.	Comments	Size
Streptomycin Sulfate, *Streptomyces sp.*	**5711**	Binds irreversibly to the 30S subunit of bacterial ribosomes and prevent the 50S ribosomal subunit from attaching to the translation initiation complex. Inhibits initiation, elongation, and termination of protein synthesis in prokaryotes and induces misreading of the genetic code.	100 g
Tetracycline, Hydrochloride	**58346**	An antibiotic that inhibits bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit, preventing binding of aminoacyl tRNA to the A-site and blocking translocation.	10 g 25 g 50 g
Tetracycline, Hydrochloride, Cell Culture-Tested	**583411**	An antibiotic that inhibits bacterial protein synthesis by reversibly binding to the 30S ribosomal subunit, preventing binding of aminoacyl tRNA to the A-site and blocking translocation.	10 g 25 g 50 g
Thiostrepton	**598226**	Inhibits bacterial protein synthesis and ribosomal GTPase activity by binding non-covalently, but virtually irreversibly, to the 23S rRNA in the GTPase center of the 50S subunit. Thiostrepton binding directly prevents elongation factor G binding to the ribosome.	1 g 10 g
Tobramycin, Free Base	**614005**	Binds irreversibly to the 30S subunit of bacterial ribosomes and prevents the 50S ribosomal subunit from attaching to the translation initiation complex.	100 mg

Sonic Hedgehog Signaling Inhibitors

Sonic hedgehog (Shh) genes are highly conserved and play an important role morphogenesis during embryonic development. Hedgehog ligands are involved in both short-range (contact dependent) and long-range signaling events. Hedgehog protein (~45-kDa) undergoes autocatalytic processing to yield a ~20-kDa N-terminal signaling domain and a ~25-kDa C-terminal catalytic domain. The C-terminal domain is responsible for the intramolecular precursor processing and acts as a cholesterol transferase. The cholesterol moiety is important in directing Shh protein traffic in secretory cells.

The Shh signaling pathway involves two transmembrane proteins known as Patched (Ptc) and Smoothened (Smo). Ptc is a twelve-pass membrane protein that binds Hedgehog ligand. Smoothened (Smo), a seven-pass membrane protein that acts as a signal transducer. In the absence of ligand, Ptc interacts with and inhibits Smo. This inhibition activates a transcriptional repressor. When ligand is present, the interaction of Ptc and Smo is altered and the inhibitory effect on Smo is removed.

Shh signaling is not only involved in *de novo* vascularization during embryonic development, but is also known to induce angiogenesis in adults. Over signaling by Shh appears to be involved in the initiation and propagation of some tumors of the muscle, skin and nervous system. Shh is shown to up-regulate VEGF-1 and -2 and angiopoietins-1 and -2.

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Sonic Hedgehog Signaling Inhibitors

Product	Cat. No.	Comments	Size
AY 9944	**190080**	A cell-permeable inhibitor of 7-dehydrocholesterol reductase (Δ7-sterol reductase). Also reported to induce a rapid and irreversible reduction in acidic-sphingomyelinase activity in fibroblasts.	5 mg
NEW Cyclopamine, *V. californicum*	**239803**	A steroidal alkaloid and cholesterol mimic that disrupts cholesterol bio-synthesis and specifically antagonizes Shh signaling through direct interaction with Smo (smoothened).	1 mg
NEW Jervine	**420210**	A cell-permeable inhibitor that induces cyclopia by blocking Shh signaling (IC_{50} = 500 –700 nM in s12 cells).	1 mg
SANT-1	**559303**	A potent antagonist of the Shh signaling (IC_{50} = 20 nM in the Shh-LIGHT2 assay and in Ptch1$^{-/-}$ cells) that acts by binding directly to Smoothened (Smo; K_d = 1.2 nM). Unlike cyclopamine (Cat. No. 239803), SANT-1 equipotently inhibits the activities of both wild-type and oncogenic Smo (IC_{50} = 30 nM in SmoA1-LIGHT2 assay).	5 mg
NEW Tomatidine, Hydrochloride	**614350**	A steroidal alkaloid that structurally resembles Cyclopamine (Cat. No. 239803), but lacks the capacity to inhibit Shh signaling.	25 mg
U18666A	**662015**	A cell-permeable, amphiphilic amino-steroid that alters intracellular membrane protein trafficking by impairing intracellular biosynthesis and transport of LDL-derived cholesterol, presumably via its inhibitory effect on 2,3-oxidosqualene-lanosterol cyclase activity. Also reported to inhibit the activity of Δ8-sterol isomerase.	10 mg

Inhibitors: Some Technical Tips

How much inhibitor should I use?

The amount of inhibitor required depends on various factors, such as target accessibility, cell permeability, duration of incubation, type of cells used, etc. It is best to survey the literature to determine the initial concentration. If published K_i or IC_{50} values are known, one should use 5 to 10 times higher than these values to maximally inhibit enzyme activity. If K_i or IC_{50} values are unknown, then one should try a wide range of inhibitor concentrations and use Michaelis-Menten kinetics to determine the K_i value. It is not unusual to see either no inhibition or even a reverse effect when high concentrations of inhibitors are used. Researchers should always run an appropriate control to eliminate non-specific effects of the solvent used to solubilize the inhibitor.

What is the difference between EC_{50}, ED_{50}, K_i, IC_{50}, and K_d?

In pharmacology and biochemistry, in order to determine the efficacy of a drug or inhibitor, the following terms are commonly used. Sometimes, confusion arises when researchers try to repeat experiments without considering the exact term used by the original investigators.

EC_{50}: Clinical efficacy of a drug (concentration required) to produce 50% of the maximum effect (may be inhibitory or stimulatory effect). This term is used usually with pharmaceuticals.

ED_{50}: Median effective dose (as opposed to concentration) at which 50% of individuals exhibit the specified quantal effect.

IC_{50}: Concentration required to produce 50% inhibition.

K_i: Inhibitor concentration at which 50% inhibition is observed (it is calculated using Michaelis-Menten kinetics).

K_d: An equilibrium constant for the dissociation of a complex of two or more biomolecules into its components; for example, dissociation of an inhibitor or substrate from an enzyme.

How much of an inhibitor or stimulator should one inject into an animal?

There is no simple answer to this question. One must optimize the dose empirically by performing a few preliminary experiments. First determine if the compound in question is cell-permeable. Also, survey the literature for any reported IC_{50}, ED_{50}, or EC_{50}, values. One may follow the sample calculation given below as a general guide:

H-89, dihydrochloride, a cell-permeable protein kinase A inhibitor, has an IC_{50} value of 48 nM. It has a molecular weight of 519.3. For H-89, 2HCl a 240 to 480 nM range of H-89 is sufficient to cause maximal inactivation of protein kinase A. To use it *in vivo* we have to make a few assumptions. If a rat weighs about 200 g and we assume that 70% of its body weight is water, the volume of distribution will be approximately 140 ml. In this case 240 nM = 240 nmoles/liter = 124.63 mg/liter. Because the volume of distribution is about 140 ml, 124.63 x 0.140 = 17.45 mg would be the required amount for injection into the rat. It is important to note that the drug distribution will vary depending on the mode of injection (intravenous, intramuscular, or intraperitoneal), bioavailability, half-life, rates of hepatic and renal clearance, binding to proteins, and tissue-specific distribution and accumulation. The specific tissue uptake may also be limited in whole organs or tissues as compared to isolated cell preparations. In whole animal studies, sometimes a loading dose is required to achieve the target concentration. This may then be followed by a sustained infusion to maintain the drug level in the blood. One must always exercise caution and not overdose the animal.

What type of solvent is best suited for dissolving a compound?

In biological experiments water is the most preferred solvent. However, several organic compounds are either not soluble in water or they degrade rapidly in the presence of moisture. If DMSO is a recommended solvent, it is best to use a fresh stock bottle of DMSO that is deemed free of any moisture. Any contaminating moisture may accelerate the degradation of compound in question or may render it insoluble.

Why can't I make serial dilutions of my DMSO stock solution directly in my buffer?

In some cases this may not be a problem. However, in most cases the organic material will precipitate out of the solution when added directly to an aqueous medium. It is best to make the initial serial dilutions only in DMSO and then add the final diluted sample to your buffer or the cell culture medium. Also, the compound may be soluble in aqueous medium only at its working concentration.

Which protein kinase inhibitor is best suited for my experiment?

If the mechanism involved in phosphorylation is unknown, a broad range inhibitor, such as Staurosporine, should be used first to determine if indeed a protein kinase is involved. Secondly, a more specific inhibitor of PKA (e.g., H-89, CN 371963, or 8-Br-cAMP, Rp isomer, CN 116816), PKC (e.g., Bisindolylmaleimide, CN 203290), or PKG (e.g., KT5823, CN 420321; or PKG inhibitor, CN 370654) should be used to eliminate the possibility of more than one kinase. To elucidate the exact mechanism involved, isozyme specific inhibitors, such as for PKC isozymes, can be used.

How can I determine if a caspase inhibitor is reversible or irreversible?

The C-terminal group determines the reversibility or the irreversibility of any caspase inhibitor. In general, caspase inhibitors with an aldehyde (CHO) group are reversible. The CMK, FMK, and FAOM groups are more reactive and form covalent bonds with the enzyme, creating an irreversible linkage. FMK is slightly less reactive than CMK and therefore is considered more specific for the enzyme site being inhibited.

What determines the specificity of a particular caspase inhibitor?

The peptide recognition sequence determines the specificity of the inhibitor for a particular caspase. Sometimes the aspartic acid residue is esterified to increase cell permeability of the peptide. VAD is a general caspase inhibitor. Earlier it was considered to be specific for caspase-1 (ICE), however, now it is considered to inhibit even caspase-3 and caspase-4. Addition of a tyrosine residue (Y) to the sequence (YVAD) makes the inhibitor more specific for caspase-1. The sequence DEVD recognizes caspase-3 and also caspases-6, -7, -8, and -10.

What are the advantages of using FMK based caspase inhibitors and how do they differ from CHO-based inhibitors?

The FMK-based caspase inhibitors covalently modify the thiol group of the enzyme making them irreversible inhibitors. Generally, at the amine end of the inhibitor we have a benzyloxycarbonyl (Z), biotin, or aceytl (Ac) group. These groups also increase hydrophobicity of the molecule, which makes them more cell-permeable. Compared to the inhibitors with an Ac or a biotin group, those inhibitors with a Z-group are even more cell-permeable. Inhibitors with a biotin group can serve as a detection tool and are useful in tagging the enzyme-inhibitor site.

The CHO-based inhibitors are reversible due to the fact that the thiol group of the enzyme forms an adduct to the carbonyl group of the aldehyde that is reversible. As a general rule CHO-based inhibitors are hydrated and hence are slow binding. The extent of their reversibility depends on the pH, metal ion concentration, and other conditions. When the aldehyde group is attached to the aspartic acid (D-CHO), the product exists as a pseudo acid aldehyde in equilibrium. This makes it somewhat cell-permeable.

What criteria should I use when selecting a protease inhibitor?

When processing cells or tissues one must assume that active proteases are present in the medium or are being secreted. Hence, it is important to include protease inhibitors even in the early steps of sample preparation. For best results add protease inhibitors to the medium just prior to use. Use of inhibitors in buffers stored over a period of time is not recommended. Different cells and tissue types exhibit different protease profiles. Serine proteases are widely distributed in all cells, bacterial cells contain higher levels of serine and metalloproteases; animal tissue extracts are rich in serine-, cysteine-, and metalloproteases, and plant extracts contain higher quantities of serine and cysteine proteases. If you are not sure of the type of proteases present in the sample, it is best to use an inhibitor cocktail available from Merck Biosciences or customize your own cocktails.

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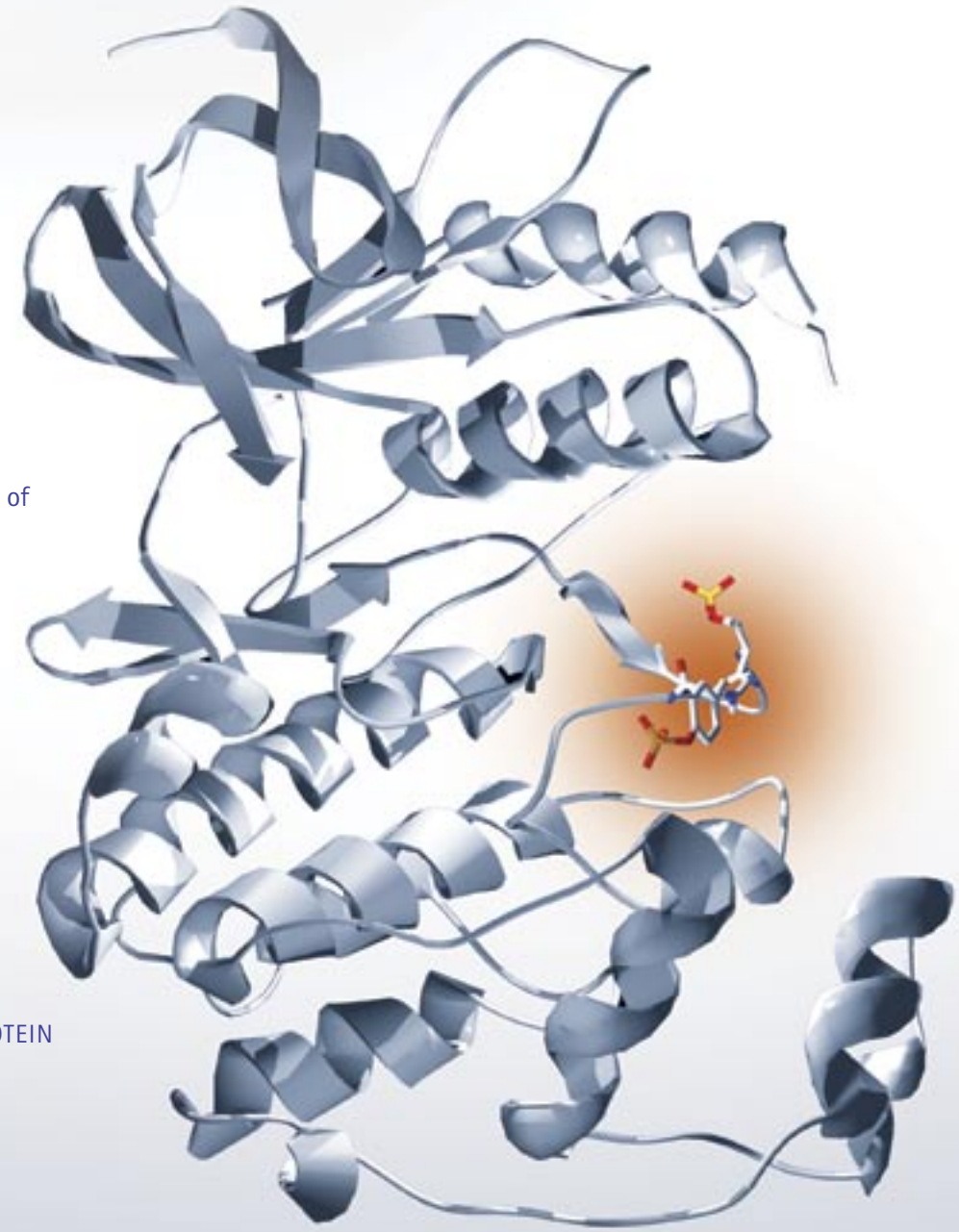

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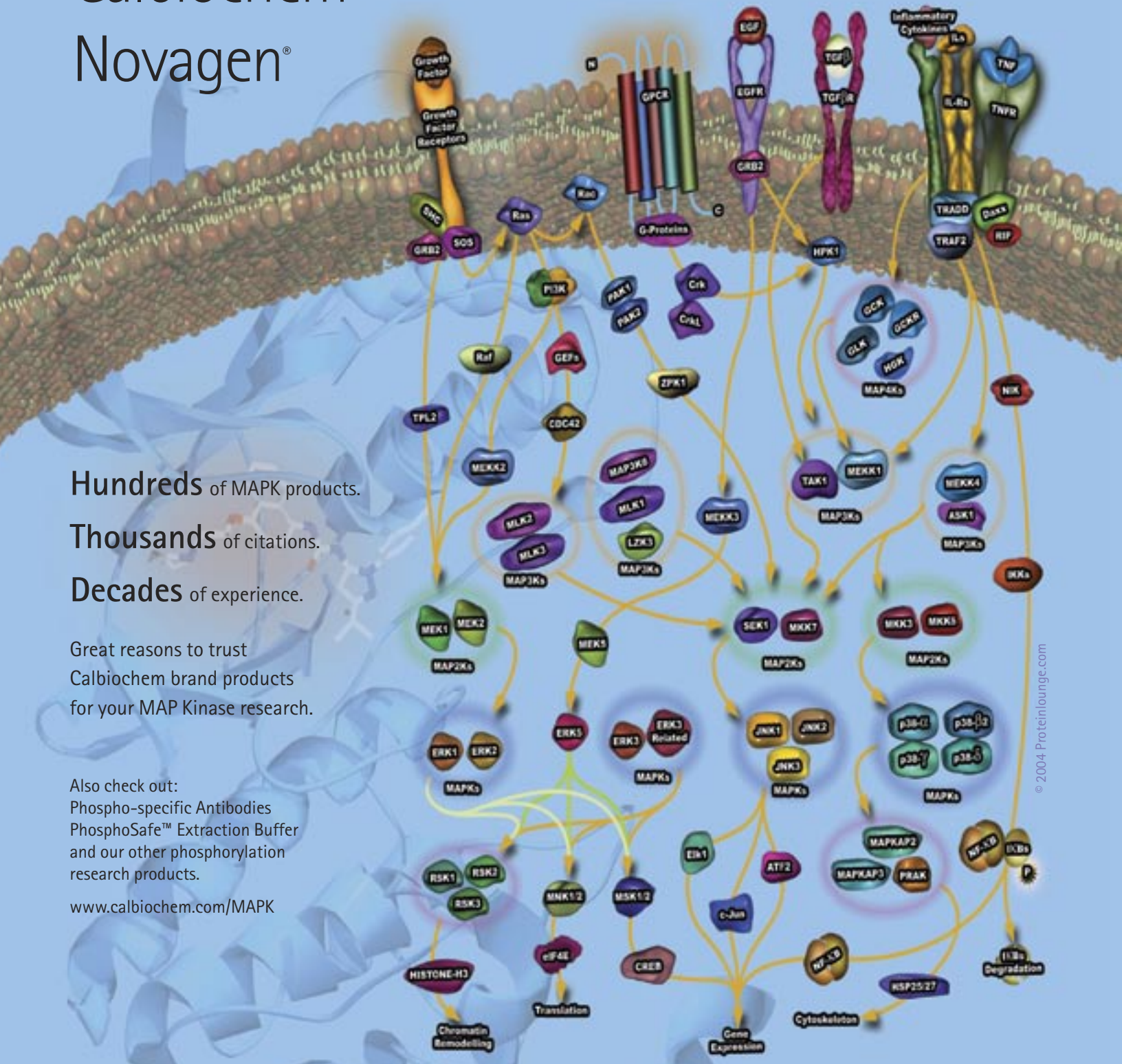

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