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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 and best understood 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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AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

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

Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	**[N-(2-Aminoethyl)-5-chloronaphthalene-1-sulfonamide, HCl]** A cell-permeable, reversible, and shorter alkyl chain derivative of W-7 that inhibits casein kinase I (K_i = 80 µM), casein kinase II (K_i = 5.1 µM), myosin light chain kinase (K_i = 7.4 µM), protein kinase A (K_i = 4.3 µM), protein kinase C (K_i = 47 µM), and protein kinase G (K_i = 3.8 µM).	10 mg
Adenosine 3',5'-cyclic Monophosphorothioate, 2'-O-Monobutyryl-, Rp-Isomer, Sodium Salt	**116825**	**(Rp-MB-cAMPS, Na)** A cell-permeable, metabolically-stable precursor of Rp-cAMPS (Cat. No.116814) that acts as a competitive inhibitor of protein kinase A type I and II. During metabolic activation by esterases, the inhibitor and butyrate are released. Reported to inhibit glucose-induced proliferation of the pancreatic ß-cell line, INS-1. More lipophilic and cell-permeable than Rp-cAMPS.	5 µmol
Adenosine 3',5'-cyclic Monophosphorothioate, 8-Bromo-, Rp-Isomer, Sodium Salt	**116816**	**(Rp-8-Br-cAMPS, Na)** A potent, cell-permeable, and reversible metabolically-stable cAMP antagonist that inhibits cAMP-dependent protein kinase and shows preference for PKA type I. More lipophilic than cAMP antagonist Rp-cAMPS (Cat. No.116814).	5 µmol
Adenosine 3',5'-cyclic Monophosphorothioate, 8-Chloro-, Rp-Isomer, Sodium Salt	**116819**	**(Rp-8-Cl-cAMPS, Na)** A cell-permeable, metabolically-stable analog of cAMP that acts as a competitive inhibitor of protein kinase A. Lipophilic analog of the cAMP antagonist Rp-cAMPS (Cat. No.116814). Preferentially inhibits type I PKA (IC_{50} = ~50 µM).	5 µmol
Adenosine 3',5'-cyclic Monophosphorothioate, Rp-Isomer, Triethylammonium Salt	**116814**	**(Adenosine 3',5'-cyclic Phosphorothioate-Rp; Rp-cAMPS, TEA)** A cell-permeable and reversible inhibitor of protein kinase A (K_i = 11 µM). Resistant to hydrolysis by phosphodiesterases. Noncompetitive with respect to ATP.	5 µmol
4-Cyano-3-methylisoquinoline	**238900**	A potent, cell-permeable, reversible, and specific inhibitor of protein kinase A (IC_{50} = 30 nM). Inhibition is competitive with respect to ATP. Shows only weak inhibitory activities against Ca^{2+}-dependent protein kinase (CDPK), MLCK, PKC, and cyclic nucleotide-binding phosphatase.	1 mg

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AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

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

Product	Cat. No.	Comments	Size
Daphnetin	**268295**	**(7,8-Dihydroxy-2H-1-benzopyran-2-one; 7,8-Dihydroxycoumarin)** A cell-permeable, substrate competitive, and reversible coumarin analog that acts as an inhibitor of several protein kinases. Inhibits EGFR kinase (IC_{50} = 7.67 µM), PKA (IC_{50} = 9.33 µM), and PKC (IC_{50} = 25 µM), *in vitro*. The inhibition of EGFR kinase by daphnetin was competitive to ATP and non-competitive to the peptide substrate. Also acts as a potent antioxidant and anti-malarial agent.	10 mg
Ellagic Acid, Dihydrate	**324683**	**(4,4',5,5',6,6'-Hexahydroxydiphenic Acid 2,6,2',6'-Dilactone)** A cell-permeable, reversible, potent antioxidant that has anti-mutagenic and anti-carcinogenic properties. Acts as a selective and ATP-competitive inhibitor of CK2 (IC_{50} = 40 nM). Moderately inhibits DNA topoisomerases I and II, Lyn, PKA catalytic subunit, Lyk, GSK-3, PKC, and FGR (IC_{50} = 1.8, 2.1, 2.9, 3.5, 4.3, 7.5, 8.0, and 9.4 µM, respectively). Only minimally inhibits DYRK1a, CSK, RET, Flt3, and NPM-ALK (IC_{50} >40 µM). Shown to act as an uncompetitive inhibitor of arginine methyltransferase CARM1 and block histone H3R17 methylation.	500 mg
H-7, Dihydrochloride	**371955**	**[1-(5-Isoquinolinesulfonyl)-2-methylpiperazine, 2HCl]** A broad-based, cell-permeable, reversible, ATP-competitive serine/threonine kinase inhibitor. Inhibits protein kinase A (K_i = 3.0 µM), myosin light chain kinase (K_i = 97 µM), protein kinase C (K_i = 6.0 µM), and protein kinase G (K_i = 5.8 µM). Induces apoptotic DNA fragmentation and cell death in HL-60 human promyelocytic leukemia cells. Also inhibits telomerase activity in quercetin-, H-89-, or herbimycin A-treated NPC-076 cells.	1 mg 5 mg
H-8, Dihydrochloride	**371958**	**{N-[2-(Methylamino)ethyl]-5-isoquinolinesulfonamide, 2HCl}** A potent, cell-permeable, reversible, and ATP-competitive inhibitor of cyclic-nucleotide-dependent protein kinases. Inhibits protein kinase A (K_i = 1.2 µM), myosin light chain kinase (K_i = 68 µM), protein kinase C (K_i = 15 µM), and protein kinase G (K_i = 480 nM).	1 mg 5 mg
InSolution™H-89, Dihydrochloride	**371962**	**{N-[2-((*p*-Bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 2HCl}** A 10 mM (1 mg/193 µl) solution of H-89, Dihydrochloride (Cat. No. 371963) in DMSO. *Not available for sale in Japan.*	1 mg
H-89, Dihydrochloride	**371963**	**{N-[2-((*p*-Bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 2HCl}** A cell-permeable, selective, reversible, ATP-competitive and potent inhibitor of protein kinase A (K_i = 48 nM). Inhibits other kinases only at much higher concentrations: CaM kinase II (K_i = 29.7 µM), casein kinase I (K_i = 38.3 µM), myosin light chain kinase (K_i = 28.3 µM), protein kinase C (K_i = 31.7 µM), and ROCK-II (IC_{50} = 270 nM). May be used to discriminate between the effects of PKA and cAMP-regulated guanine-nucleotide-exchange factors (GEFs) such as GEFI, GEFII, or Epac (exchange protein directly activated by cAMP). Enhances radiation-induced apoptosis in the human cell line BM 13674. A 10 mM (1 mg/193 µl) solution of H-89, 2HCl (Cat. No.371962) in DMSO is also available.	1 mg
H-9, Dihydrochloride	**371961**	**[N-(2-Aminoethyl)-5-isoquinolinesulfonamide, 2HCl]** Closely resembles H-8 in chemical structure and inhibitory potency. A cell-permeable, reversible, and ATP-competitive inhibitor of protein kinase A (K_i = 1.9 µM), protein kinase C (K_i = 18 µM), and protein kinase G (K_i = 870 nM). Useful as a ligand for separation and purification of these enzymes.	1 mg
HA 1004, Dihydrochloride	**371964**	**[N-(2-Guanidinoethyl)-5-isoquinolinesulfonamide, 2HCl]** A cell-permeable, reversible, and ATP-competetive inhibitor of protein kinase A (K_i = 2.3 µM), CaM kinase II (K_i = 13 µM), myosin light chain kinase (K_i = 150 µM), protein kinase C (K_i = 40 µM), and protein kinase G (K_i = 1.3 µM). An intracellular Ca^{2+} antagonist with no effect on cardiac function. Causes selective pulmonary vasodilation during pulmonary hypertension.	1 mg
HA 1077, Dihydrochloride	**371970**	**[Fasudil; (5-Isoquinolinesulfonyl)homopiperazine, 2HCl]** A cell-permeable, reversible, and ATP-competitive Ca^{2+} antagonist with anti-vasospastic properties. Inhibits protein kinase A (K_i = 1.6 µM), protein kinase G (K_i = 1.6 µM), and myosin light chain kinase (K_i = 36 µM). Also reported to potently inhibit Rho-associated kinase (ROCK; IC_{50} = 10.7 µM). Prevents apoptosis and enhances the survival and cloning efficiency of dissociated hES cells without affecting their pluripotency.	1 mg
InSolution™K-252a, *Nocardiopsis* sp.	**420297**	A 1 mM (100 µg/214 µl) solution of K-252a (Cat. No. 420298) in anhydrous DMSO.	100 µg

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

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

Product	Cat. No.	Comments	Size
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable, reversible, and ATP-competitive inhibitor against multiple protein kinases, including, but not limited to, CaM kinase II (K_i = 1.8 nM), myosin light chain kinase (K_i = 20 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), protein kinase G (K_i = 20 nM), NGF receptor gp140^{trk} (IC_{50} = 3 nM), its transforming *trk* oncogenes, and the related neurotrophin receptors gp145^{trkB} and gp145^{trkC}. Reported to induce apoptosis and cell cycle arrest by decreasing Cdk1 and Cdc25c activity in T98G cells and inhibit Flt3 phosphorylation in Flt3/Itd-BaF3 cells (IC_{50} <50 nM). Also available as a premade 1 mM (100 µg/214 µl) solution in DMSO (Cat. No.420297).	100 µg
K-252b, *Nocardiopsis* sp.	**420319**	A cell-permeable, reversible, ATP-competitive, and non-selective inhibitor of protein kinase C (K_i = 20 nM), myosin light chain kinase (K_i = 147 nM), protein kinase A (K_i = 90 nM), and protein kinase G (K_i = 100 nM).	50 µg 100 µg
KT5720	**420320**	A potent, specific, cell-permeable, reversible and ATP-competitive inhibitor of protein kinase A (K_i = 56 nM) that is prepared by a chemical modification of K-252a. Does not significantly affect the activities of PKC, PKG, and MLCK. Inhibits axon branching in cultured neurons. A 2 mM (50 µg/47 µl) solution of KT 5720 (Cat. No.420323) in DMSO is also available.	50 µg 100 µg
InSolution™KT5720	**420323**	A 2 mM (50 µg/47 µl) solution of KT5720 (Cat. No. 420320) in anhydrous DMSO.	50 µg
Piceatannol	**527948**	**(*trans*-3,3',4,5'-Tetrahydroxystilbene)** A cell-permeable, substrate competitive and reversible plant metabolite that inhibits the activity of rat liver protein kinase A catalytic subunit (IC_{50} = 3 µM), PKC (IC_{50} = 8 µM), MLCK (IC_{50} = 12 µM). In RBL-2H3 cells, the selective inhibition of Syk by piceatannol results in inhibition of FceR1-mediated signaling. Also inhibits wheat embryo Ca^{2+}-dependent protein kinase (CDPK) (IC_{50} = 19 µM), and p72^{syk} (IC_{50} = 10 µM), a non-receptor tyrosine kinase, relative to Lyn in isolated enzyme preparations. Also possesses anti-leukemic properties. Reported to activate sirtuins and promote the survival of eukaryotic cells.	1 mg
Protein Kinase A Inhibitor 14-22 Amide, Cell-Permeable, Myristoylated	**476485**	**(Myr-GRTGRRNAI-NH_2; Myristoylated Protein Kinase A Inhibitor Amide 14-22, Cell-Permeable; PK_i 14-22 Amide, Cell-Permeable)** 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 a highly specific inhibitor (K_i = 36 nM) of cAMP-dependent protein kinase.	500 µg
Protein Kinase A Inhibitor 5-24	**116805**	**(H-TTYADFIASGRTGRRNAIHD)** A potent synthetic peptide that is a competitive inhibitor of protein kinase A (K_i = 2.3 nM). Its sequence is derived from the heat-stable skeletal muscle inhibitor protein of PKA. Binds to the catalytic subunit of PKA and displaces the regulatory subunit. Mimics the protein substrate by binding to the catalytic site via the arginine-cluster basic substrate.	500 µg
Protein Kinase A Inhibitor 6-22 Amide	**539684**	**(PK_i 6-22 Amide, PKA Inhibitor; TYADFIASGRTGRRNAI-NH_2)** A potent and competitive inhibitor of protein kinase A (K_i = 1.7 nM).	1 mg
InSolution™Staurosporine, *Streptomyces* sp.	**569396**	A 1 mM (100 µg/214 µl) solution of Staurosporine, *Streptomyces* sp. (Cat. No. 569397) in anhydrous DMSO.	100 µg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable, reversible, ATP-competitive and broad spectrum inhibitor of protein kinases. Inhibits protein kinase A (IC_{50} = 7 nM), CaM kinase (IC_{50} = 20 nM), myosin light chain kinase (IC_{50} = 1.3 nM), protein kinase C (IC_{50} = 700 pM), and protein kinase G (IC_{50} = 8.5 nM). Also inhibits platelet aggregation induced by collagen or ADP but has no effect on thrombin-induced platelet aggregation. Induces apoptosis in human malignant glioma cell lines. Arrests normal cells at the G_1 checkpoint. A 1 mM (100 µg/214 µl) solution of Staurosporine (Cat. No.569396) in DMSO is also available.	100 µg 250 µg
TX-1123	**655200**	**[2-((3,5-di-*tert*-Butyl-4-hydroxyphenyl)-methylene)-4-cyclopentene-1,3-dione]** A cell-permeable, reversible, and substrate-competitive arylidene-cyclopentenedione derived tyrphostin that acts as an inhibitor for Src, eEF2-K, and PKA (IC_{50} = 2.2, 3.2, and 9.6 µM, respectively), while it inhibits EGFR-K and PKC at much higher concentrations (IC_{50} = 320 µM). Displays potent antitumor activity (EC_{50} = 3.66 and 39 µM in HepG2 and HCT116 tumor cells, respectively) with greatly reduced mitochondrial- (≥1000-fold) and hepato-toxicity (≥50-fold) when compared with another tyrphostin, AG 17 (Cat. No.658425). It is therefore a more promising candidate as a therapeutic agent for cancer treatment.	10 mg

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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, β1, β2, 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.

All PKC isoforms show different distribution among various cells. The α, δ, and ζ isoforms are found in all cells. The γ isoform is found only in neuronal cells. The β, ε, and λ isoforms are found in various tissues, whereas η and τ isoforms are predominantly found in epithelial and immune cells.

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 phospholipidbinding 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. Downregulation of PKC_α 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. Generation of isozyme-specific tools have increased our understanding of the contribution of specific PKC isozymes to various cellular functions. For example, PKCα, ε, and λ promote cell proliferation and PKCδ is involved in apoptotic cell death.

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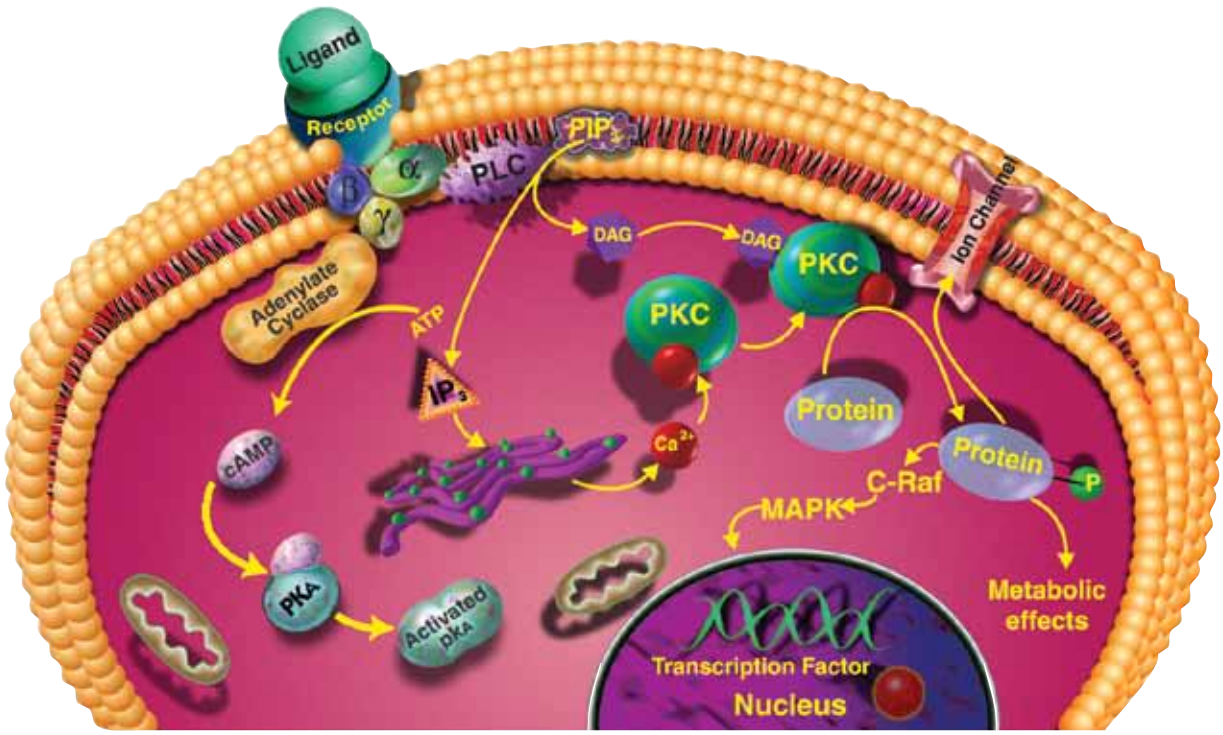

Isozyme Specificities of Selected Protein Kinase C Inhibitors (IC_{50} values are in µM)

Product	Cat. No.	PKC_{α}	PKC_{β}	$PKC_{\beta I}$	$PKC_{\beta II}$		PKC_{γ}	PKC_{δ}	PKC_{ε}	PKC_{μ}	PKC_{η}	Ref.
Bisindolylmaleimide I (Gö 6850)	**203290**	0.008	–	0.018	–	–	0.21	0.132	5.8	–	–	1
CGP41251	**539648**	0.024	–	0.017	0.032	0.018	0.360	4.50	>1000	–	0.060	2
Gö 6976	**365250**	0.0023	–	0.006	–	–	–	–	–	0.02	–	1
Gö 6983	**365251**	0.007	0.007	–	–	0.006	0.01	–	0.06	20	–	3
LY333531	**–**	0.360	–	0.0047	0.0059	0.400	0.250	0.600	$>10^5$	–	0.052	4
PKCβ Inhibitor	**539654**	0.331	–	0.021	0.005	> 1.0	–	2.8	–	–	–	5
Ro-31-7549	**557508**	0.053		0.195	0.163	0.213	–	0.175	–	–	–	6
Ro-31-8220	**557520**	0.005	–	0.024	0.014	0.027	–	0.024	–	–	–	6
Ro-31-8425	**557514**	0.008	–	0.008	0.014	0.013	–	0.039	–	–	–	6
Ro-32-0432	**557525**	0.009	–	0.028	0.031	0.037	–	0.108	–	–	–	6
Rottlerin	**557370**	30	42	–	–	40	3 - 6	100	100	–	–	7
Staurosporine	**569397**	0.028	–	0.013	0.011	0.032	0.028	0.025	>1.5	–	–	6
UCN01	**539644**	0.029	–	0.034	–	0.030	0.590	0.530	–	–	–	8

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AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

Protein Kinase C (PKC) Inhibitors

Product	Cat. No.	Comments	Size
Bisindolylmaleimide I	**203290**	**{2-[1-(3-Dimethylaminopropyl)-1H-indol-3-yl]-3-(1H-indol-3-yl)-maleimide; Gö 6850; GF 109203X}** A highly selective, cell-permeable, and reversible protein kinase C (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-, $ß_I$-, $ß_{II}$-, γ-, δ-, and - isozymes. Potently inhibits GSK-3 in primary adipocyte lysates (IC_{50} = 360 nM) and in GSK-3ß immunoprecipitates (IC_{50} = 170 nM). May inhibit protein kinase A at a much higher concentration (K_i = 2 µM). A 1 mg/ml solution of Bisindolylmaleimide I (Cat. No. 203293) in anhydrous DMSO is also available.	250 µg 1 mg
InSolution™Bisindolylmaleimide I	**203293**	**{2-[1-(3-Dimethylaminopropyl)-1H-indol-3-yl]-3-(1H-indol-3-yl)-maleimide; Gö 6850}** A 1 mg/ml solution of Bisindolylmaleimide I (Cat. No. 203290) in anhydrous DMSO.	1 ml
Bisindolylmaleimide I, Hydrochloride	**203291**	**{2-[1-(3-Dimethylaminopropyl)-1H-indol-3-yl]-3-(1H-indol-3-yl)maleimide, HCl}** An enhanced water-soluble form of Bisindolylmaleimide I (Cat. No.203290). A reversible and ATP-competitive inhibitor of protein kinase C (K_i = 10 nM). May inhibit protein kinase A at much higher concentrations (K_i = 2 µM).	250 µg 1 mg
Bisindolylmaleimide II	**203292**	**{2-[1-[2-(1-Methylpyrrolidino)ethyl]-1H-indol-3-yl]-3-(1H-indol-3-yl)maleimide}** A potent, cell permeable, reversible, ATP-competitive and selective inhibitor of protein kinase C (IC_{50} = 13 nM). May inhibit protein kinase A at much higher concentrations (IC_{50} = 2 µM).	1 mg
Bisindolylmaleimide III, Hydrochloride	**203294**	**{2-[1-(3-Aminopropyl)-1H-indol-3-yl]-3-(1H-indol-3-yl)maleimide, HCl}** A potent, cell-permeable, reversible, ATP-competitive and selective inhibitor of protein kinase C (IC_{50} = 26 nM). May inhibit protein kinase A at much higher concentrations (IC_{50} = 500 nM).	250 µg 1 mg
Bisindolylmaleimide IV	**203297**	**Arcyriarubin A** A potent, cell permeable, and selective inhibitor of protein kinase C (IC_{50} = 87 nM). Inhibits protein kinase A at much higher concentrations (IC_{50} = 2.7 µM).	1 mg
Bisindolylmaleimide V	**203303**	**[2,3-*bis*(1H-Indol-3-yl)-N-methylmaleimide; Ro 31-6045]** A cell-permeable negative control compound for protein kinase C inhibition studies (IC_{50} >100 µM). Blocks the activation of mitogen-stimulated protein kinase $p70^{s6k}/p85^{s6k}$ *in vivo* (IC_{50} 8 µM).	250 µg 1 mg

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AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

Protein Kinase C (PKC) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Calphostin C, *Cladosporium cladosporioides*	**208725**	**(UCN-1028c)** A cell permeable, highly specific inhibitor of protein kinase C (IC_{50} = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. Does not compete with Ca^{2+} or phospholipids. At higher concentrations inhibits myosin light chain kinase (IC_{50} > 5 µM), protein kinase A (IC_{50} > 50 µM), protein kinase G (IC_{50} > 25 µM), and $p60^{v\text{-}src}$ (IC_{50} > 50 µM). Induces apoptotic DNA fragmentation and cell death in HL-60 human promyelocytic leukemia cells. Requires brief exposure to light for activation.	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 the sarcolemmal Ca^{2+}/Mg^{2+}-ATPase. Its action is strongly potentiated by phospholipase A_2. Inhibits protein kinase C (IC_{50} = 1.8 µM). *Not available for sale outside the United States.*	1 mg
Chelerythrine Chloride	**220285**	Naturally-occurring alkaloid. Potent, selective, and cell-permeable inhibitor of protein kinase C (IC_{50} = 660 nM). Acts on the catalytic domain of PKC. 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). Inhibits thromboxane formation and phosphoinositide metabolism in platelets. Also induces apoptotic DNA fragmentation and cell death in HL-60 human promyelocytic leukemia cells.	5 mg
D-*erythro*-Sphingosine, Dihydro-	**300230**	**(Sphinganine)** Biosynthetic precursor of sphingosine. Inhibits protein kinase C (PKC) in Chinese hamster ovary cells (IC_{50} = 2.8 µM). Also directly inhibits phospholipase A_2 (PLA_2) and phospholipase D (PLD).	10 mg
D-*erythro*-Sphingosine, Free Base, High Purity	**567726**	**(trans-D-erythro-2-Amino-4-octadecene-1,3-diol; Ceramide; Cerebroside)** Highly purified preparation of bovine brain sphingosine containing >99% of the *erythro* isomer.	10 mg
D-*erythro*-Sphingosine, N,N-Dimethyl-	**310500**	A cell-permeable and reversible inhibitor of protein kinase C (PKC; IC_{50} = 12 µM) and stimulates Src kinase activity. Useful for inhibiting cell surface expression of selectins that promote adhesion of leukocytes or tumor cells to platelets and endothelial cells. Induces apoptosis in human leukemia HL-60 cells. An inhibitor of sphingosine kinase.	5 mg
Dequalinium Chloride	**263225**	**(DECA)** An antitumor agent and protein kinase C (PKC) inhibitor. When exposed to UV light, DECA covalently binds to and irreversibly inhibits PKC_α and PKC_β (IC_{50} = 7-18 µM). A potent and selective non-peptide blocker of the apamin-sensitive small conductance Ca^{2+}-activated K^+ channel (IC_{50} = 1.1 µM). A blocker of ganglionic transmission (EC_{50} = 2 µM). Selectively accumulates within the mitochondria of carcinoma cells and disrupts energy production.	500 mg
Ellagic Acid, Dihydrate	**324683**	**(4,4',5,5',6,6'-Hexahydroxydiphenic Acid 2,6,2',6'-Dilactone)** A cell-permeable, reversible, potent antioxidant that has anti-mutagenic and anti-carcinogenic properties. Acts as a selective and ATP-competitive inhibitor of CK2 (IC_{50} = 40 nM). Moderately inhibits DNA topoisomerases I and II, Lyn, PKA catalytic subunit, Lyk, GSK-3, PKC, and FGR (IC_{50} = 1.8, 2.1, 2.9, 3.5, 4.3, 7.5, 8.0, and 9.4 µM, respectively). Only minimally inhibits DYRK1a, CSK, RET, Flt3, and NPM-ALK (IC_{50} >40 µM). Shown to act as an uncompetitive inhibitor of arginine methyltransferase CARM1 and block histone H3R17 methylation.	500 mg
Gö 6976	**365250**	**[12-(2-Cyanoethyl)-6,7,12,13-tetrahydro-13-methyl-5-oxo-5H-indolo(2,3-a) pyrrolo (3,4-c)-carbazole; Go 6976]** A cell-permeable, reversible, and ATP-competitive inhibitor of protein kinase C (PKC; IC_{50} = 7.9 nM for rat brain). Selectively inhibits Ca^{2+}-dependent PKC α-isozyme (IC_{50} = 2.3 nM) and $PKC_{\beta I}$ (IC_{50} = 6.2 nM). Does not affect the kinase activity of the Ca^{2+}-independent PKC δ-, -, and ζ-isozymes even at micromolar levels. Reported to inhibit PKC_μ at higher concentrations (IC_{50} = 20 nM). A 500 µg/ml solution of Gö 6976 (Cat. No. 365253) in anhydrous DMSO is also available.	500 µg
InSolution™Gö 6976	**365253**	**[12-(2-Cyanoethyl)-6,7,12,13-tetrahydro-13-methyl-5-oxo-5H-indolo(2,3-a) pyrrolo (3,4-c)-carbazole; Go 6976, Solution]** A 500 mg/ml solution of Gö 6976 (Cat. No. 365250) in anhydrous DMSO.	1 ml
Gö 6983	**365251**	**{2-[1-(3-Dimethylaminopropyl)-5-methoxyindol-3-yl]-3-(1H-indol-3-yl) maleimide; Go 6983}** A potent, cell-permeable, reversible, and ATP-competitive inhibitor of protein kinase C (PKC) that inhibits several PKC isozymes (IC_{50} = 7 nM for PKC_α and PKC_β; 6 nM for PKC_γ; 10 nM for PKC_δ; and 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

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

Protein Kinase C (PKC) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Gö 7874, Hydrochloride	**365252**	A cell-permeable, potent, reversible, ATP-competitive, and selective inhibitor of protein kinase C (IC_{50} = 4 nM for rat brain PKC). Inhibits protein kinase A (IC_{50} = 510 nM), protein kinase G (IC_{50} = 4.8 µM), and myosin light chain kinase (IC_{50} = 120 nM) at much higher concentrations.	500 µg
H-7, Dihydrochloride	**371955**	**[1-(5-Isoquinolinesulfonyl)-2-methylpiperazine, 2HCl]** A broad-based, cell-permeable, reversible, ATP-competitive serine/threonine kinase inhibitor. Inhibits protein kinase A (K_i = 3.0 µM), myosin light chain kinase (K_i = 97 µM), protein kinase C (K_i = 6.0 µM), and protein kinase G (K_i = 5.8 µM). Induces apoptotic DNA fragmentation and cell death in HL-60 human promyelocytic leukemia cells. Also inhibits telomerase activity in quercetin-, H-89-, or herbimycin A-treated NPC-076 cells.	1 mg 5 mg
HBDDE	**372770**	**(2,2',3,3',4,4'-Hexahydroxy-1,1'-biphenyl-6,6'-dimethanol Dimethyl Ether)** A cell-permeable protein kinase C (PKC) inhibitor 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 in *in vitro* assays. Reported to induce apoptosis in rodent cerebellar granule neurons.	1 mg
Hispidin	**377980**	**[6-(3,4-Dihydroxystyrl)-4-hydroxy-2-pyrone]** A potent, cell permeable, and reversible inhibitor of protein kinase C_β isoform (PKC_β; IC_{50} = 2 µM). Has stronger cytotoxic effects on cancer cells than on normal cells *in vitro*.	2 mg
Hypericin	**400076**	Polycyclic dione that has anti-retroviral activity. Inhibits protein kinase C (IC_{50} = 3.3 µM). Also known to inhibit casein kinase II (IC_{50} = 6 nM), MAP kinase (IC_{50} = 4 nM), and the protein tyrosine activities of the insulin receptor (IC_{50} = 20-29 nM) and the epidermal growth factor receptor (IC_{50} = 35 nM).	1 mg
InSolution™ K-252a, *Nocardiopsis* sp.	**420297**	A 1 mM (100 µg/214 µl) solution of K-252a (Cat. No. 420298) in anhydrous DMSO.	100 µg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable, reversible, and ATP-competitive inhibitor against multiple protein kinases, including, but not limited to, CaM kinase II (K_i = 1.8 nM), myosin light chain kinase (K_i = 20 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), protein kinase G (K_i = 20 nM), NGF receptor $gp140^{trk}$ (IC_{50} = 3 nM), its transforming *trk* oncogenes, and the related neurotrophin receptors $gp145^{trkB}$ and $gp145^{trkC}$. Reported to induce apoptosis and cell cycle arrest by decreasing Cdk1 and Cdc25c activity in T98G cells and inhibit Flt3 phosphorylation in Flt3/Itd-BaF3 cells (IC_{50} <50 nM). Also available as a premade 1 mM (100 µg/214 µl) solution in DMSO (Cat. No.420297).	100 µg
K-252b, *Nocardiopsis* sp.	**420319**	A cell-permeable, reversible, ATP-competitive, and non-selective inhibitor of protein kinase C (K_i = 20 nM), myosin light chain kinase (K_i = 147 nM), protein kinase A (K_i = 90 nM), and protein kinase G (K_i = 100 nM).	50 µg 100 µg
K-252c	**420305**	A cell-permeable, reversible, and ATP-competitive inhibitor of protein kinase C (IC_{50} = 2.45 µM) and protein kinase A (IC_{50} = 25.7 µM).	1 mg
Melittin	**444605**	A 26-residue polypeptide from bee venom that binds calmodulin in a Ca^{2+}-dependent manner. A stimulator of $G_i\alpha$ and $G_{i1}\alpha$ activity that is reported to inhibit adenylate cyclase activity in synaptic membranes. Activates phospholipase A_2 and inhibits protein kinase C (IC_{50} = 5-7 µM) by binding to the catalytic domain in a Mg^{2+}-ATP sensitive manner. Has also been used for affinity purification of several Ca^{2+}-binding proteins.	250 µg
NGIC-I	**481500**	**(Non-glycosidic Indolocarbazole I)** A potent, cell-permeable, reversible, ATP-competitive, and selective inhibitor of protein kinase C (IC_{50} = 75 nM) versus protein kinase A (IC_{50} > 10 µM) and protein kinase G (IC_{50} = 320 nM).	500 µg
Phloretin	**524488**	**(2',4',6'-Trihydroxy-3-*p*-hydroxyphenylpropiophenone)** A cell-permeable inhibtor of protein kinase C (IC_{50} = 20-50 µM). Activates Ca^{2+}-activated K^+ channels in amphibian myelinated nerve fibers at micromolar concentrations. An inhibitor of *myo*-inositol uptake. Also inhibits L-type Ca^{2+} channel activity. A potent inhibitor of 5'-iodothyronine deiodinase. Antagonist of prostaglandin $F_{2\alpha}$ receptors linked to phospholipase C in astrocytes.	200 mg
Piceatannol	**527948**	**(*trans*-3,3',4,5'-Tetrahydroxystilbene)** A cell-permeable, substrate competitive and reversible plant metabolite that inhibits the activity of rat liver protein kinase A catalytic subunit (IC_{50} = 3 µM), PKC (IC_{50} = 8 µM), MLCK (IC_{50} = 12 µM). In RBL-2H3 cells, the selective inhibition of Syk by piceatannol results in inhibition of FceR1-mediated signaling. Also inhibits wheat embryo Ca^{2+}-dependent protein kinase (CDPK) (IC_{50} = 19 µM), and $p72^{syk}$ (IC_{50} = 10 µM), a non-receptor tyrosine kinase, relative to Lyn in isolated enzyme preparations. Also possesses anti-leukemic properties. Reported to activate sirtuins and promote the survival of eukaryotic cells.	1 mg

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

Protein Kinase C (PKC) Inhibitors *continued*

Product	Cat. No.	Comments	Size
PKC Inhibitor Set	**539573**	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 1 mg of Ro-32-0432 (Cat. No.557525). Supplied with a data sheet.	1 set
PKC_{β} Inhibitor	**539654**	**[3-(1-(3-Imidazol-1-ylpropyl)-1H-indol-3-yl)-4-anilino-1H-pyrrole-2,5-dione]** An anilino-monoindolylmaleimide compound that acts as a potent, cell-permeable, reversible, and ATP-competitive inhibitor of PKC_{β} isozymes (IC_{50} = 5 nM and 21 nM for human $PKC_{\beta II}$ and $_{\beta I}$) and displays greater selectivity over $PKC_{\alpha, \gamma \& t}$ (IC_{50} = 331 nM, > 1 µM, and 2.8 µM, respectively).	500 µg
$PKC_{\beta II}$/EGFR Inhibitor	**539652**	A cell-permeable symmetrical phthalimide compound that acts as a potent, reversible, and ATP-competitive inhibitor of EGFR and PKC isozymes α, βI, and βII (IC_{50} = 0.7 µM, 1.9 µM, 3.8 µM, and 0.41 µM, respectively). Only weakly inhibits the activity of a panel of 16 other kinases, including novel and atypical PKC isozymes. Reported to inhibit insulin-stimulated cellular 2-deoxyglucose uptake, osteoclast differentiation, ERK activation, and TLS/FUS DNA-binding activity *in vitro*. Also reported to exhibit antitumor activity in mice *in vivo*.	2 mg
Polymyxin B Sulfate	**5291**	**(Aerosporin)** An antibiotic that inhibits phospholipid-sensitive Ca^{2+}-dependent protein kinases. Mixture of polymyxin B_1 sulfate and polymyxin B_2 sulfate. Binds to cell wall and makes it more permeable, causing fluid uptake. Effective against Gram-negative bacteria.	500 mg 1 g 5 g
Protein Kinase C Inhibitor 20-28, Cell-Permeable, Myristoylated	**476480**	**(Myr-N-FARKGALRQ-NH_2; Myristoylated Protein Kinase C Inhibitor 20-28, Cell-Permeable)** Pseudosubstrate sequence from protein kinase C_{α} and ß (PKC_{α} and PKC_{β}). N-Terminus is myristoylated to allow membrane permeability. Highly specific, reversible, and substrate competitive 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 Inhibitor Peptide 19-31	**5234904**	**(PKC 19-31; RFARKGALRQKNV)** More potent, reversible, and substrate competitive inhibitor of PKC (IC_{50} = 100 nM) than PKC Inhibitor 19-36 (Cat. No.539560). Inhibits both autophosphorylation and protein substrate phosphorylation.	1 mg 5 mg
Protein Kinase C Inhibitor Peptide 19-36	**539560**	**(PKC 19-36; RFARKGALRQKNVHEVKN)** Acts as pseudosubstrate by binding to the active sites of protein kinase C. A potent, reversible, and substrate competitive inhibitor of protein kinase C (K_i = 147 nM) but not of protein kinase A (IC_{50} = 423 µM).	500 µg 1 mg
Protein Kinase C Inhibitor, EGF-R Fragment 651-658, Myristoylated	**476475**	**[Myr-N-RKRTLRRL-OH; Myristoylated EGF-R Fragment (651-658), PKC Inhibitor]** Epidermal growth-factor receptor (EGF-R) conserved sequence which is identical to v-ErbB (95-102). An N-terminal myristoylated membrane-permeable, reversible, and substrate competitive inhibitor of protein kinase C (IC_{50} = 5 µM).	500 µg
Protein Kinase C_{η} Pseudosubstrate Inhibitor, Myristoylated	**539604**	**(Myr-TRKRQRAMRRRVHQING-NH_2)** A cell-permeable, myristoylated, pseudo-substrate, reversible and substrate competitive inhibitor of the protein kinase C_{η} isozyme. Useful for studies of PKC_{η} function in intact cells.	500 µg
Protein Kinase C_{θ} Pseudosubstrate Inhibitor, Myristoylated	**539636**	**(Myr-LHQRRGAIKQAKVHHVKC-NH_2)** A cell-permeable, reversible, substrate competitive, myristoylated form of the inhibitor of protein kinase C_{θ} isozyme pseudosubstrate inhibitor (Cat. No.539634).	500 µg
Protein Kinase C_{ζ} Pseudosubstrate Inhibitor	**539610**	**(SIYRRGARRWRKL)** A selective, reversible, and substrate competitive inhibitor of protein kinase C_{ζ} and protein kinase C_{ι} ($PKC_{\zeta/\iota}$) isozymes.	500 µg
Protein Kinase C_{ζ} Pseudosubstrate Inhibitor, Myristoylated	**539624**	**(Myr-SIYRRGARRWRKL-OH)** A cell-permeable, reversible, substrate competitive, myristoylated form of the protein kinase C_{ζ} isozyme pseudosubstrate inhibitory (Cat. No.539610).	500 µg
Protein Kinase C Translocation Inhibitor Peptide	**539522**	**(EAVSLKPT; PKC Translocation Inhibitor Peptide)** An octapeptide that selectively inhibits the translocation of protein kinase C to subcellular sites in a reversible manner. Inhibition of PKC translocation is known to specifically block phorbol ester- or norepinephrine-mediated regulation of contraction in cardiomyocytes.	5 mg
Protein Kinase C Translocation Inhibitor Peptide, Negative Control	**539542**	**(LSETKPAV)** A scrambled peptide with an identical amino acid composition to that of Protein Kinase C Translocation Inhibitor Peptide (Cat. No.539522). Useful as a negative control for this PKC translocation inhibitor.	5 mg

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

Protein Kinase C (PKC) Inhibitors *continued*

Product	Cat. No.	Comments	Size
RIM-1	**557325**	**Rhodamine-conjugated Bisindolylmaleimide Inhibitor** Fluorescent probe for protein kinase C (PKC). Binds to the catalytic site of all PKC enzymes. Provides a rapid and simple means for visualizing the distribution of PKC in cells. An effective PKC inhibitor (IC_{50} = 3.3 µM for PKC_{α}; IC_{50} = 30 µM for PKA). May require cell permeabilization.	250 µg
Ro-31-7549	**557508**	**{2-[1-3(Aminopropyl)indol-3-yl]-3(1-methyl-1H-indol-3-yl) maleimide, Acetate; Bisindolylmaleimide VIII, Acetate}** A cell permeable, reversible, selective protein kinase C (PKC) inhibitor (IC_{50} = 158 nM for rat brain PKC) that acts at the ATP binding site of PKC. Does not inhibit the tyrosine phosphorylation or the activation of phospholipase $C\gamma_1$. Exhibits some degree of PKC isozyme specificity (IC_{50} = 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). Inhibits carbachol-evoked noradrenaline release (IC_{50} = 600 nM).	1 mg
Ro-31-8220	**557520**	**{3-[1-[3-(Amidinothio)propyl-1H-indol-3-yl]-3-(1-methyl-1H-indol-3-yl)maleimide; Bisindolylmaleimide IX, Methanesulfonate}** A cell-permeable, reversible, competitive, and selective inhibitor of protein kinase C (PKC; IC_{50} = 10 nM) over CaM kinase II (IC_{50} = 17 µM) and protein kinase A (IC_{50} = 900 nM). Potently inhibits GSK-3 in primary adipocytes (IC_{50} = 6.8 nM) and in GSK-3ß immunoprecipitates (IC_{50} = 2.8 nM). An inhibitor of MAP kinase phosphatase-1 expression and an activator of JNK1. Inhibits the phosphorylation of Raf-1 and induces apoptosis, independent of its effects on PKC, in HL-60 cells. Also inhibits sirtuin in a NAD-competitive manner (IC_{50} = 3.5 µM and 0.8 µM for SIRT1 and SIRT2, respectively), and induces hyperacetylation of tubulin in A549 cells. A 5 mM (500 µg/181 µl) solution of Ro-31-8220 (Cat. No.557521) in H_2O is also available.	500 µg
InSolution™Ro-31-8220	**557521**	**{3-[1-[3-(Amidinothio)propyl-1H-indol-3-yl]-3-(1-methyl-1H-indol-3-yl)maleimide; Bisindolylmaleimide IX, Methanesulfonate}** A 5 mM (500 µg/181 µl) solution of Ro-31-8220 (Cat. No. 557520) in H_2O.	500 µg
Ro-31-8425	**557514**	**{2-[8-(Aminomethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-3-yl]-3-(1-methyl-1H-indol-3-yl)maleimide, HCl; Bisindolylmaleimide X, HCl}** A potent, cell-permeable, reversible, ATP-competitive, and selective protein kinase C inhibitor (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).	1 mg
Ro-32-0432	**557525**	**3-(8-((dimethylamino)methyl)-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-10-y1)-4-(1-methyl-1*H*-indol-3-y1)-1*H*-pyrrole-2,5-dione hydrochloride, Bisindolylmaleimide XI, HCL, 2-{8-[(Dimethylamino)methyl]-6,7,8,9-tetrahydropyrido[1,2-a]indol-3-yl}-3-(1-methyl-1H-indol-3-yl)maleimide, HCl** A selective cell-permeable protein kinase C inhibitor. Displays about 10-fold greater selectivity for PKC_{α} (IC_{50} = 9 nM) and 4-fold greater selectivity for $PKC_{\beta I}$ (IC_{50} = 28 nM) over PKC (IC_{50} = 108 nM). Also prevents T cell-driven chronic inflammatory responses *in vivo*.	500 µg 1 mg
Rottlerin	**557370**	**(Mallotoxin)** A cell-permeable and reversible protein kinase C inhibitor that exhibits greater selectivity for PKC_{δ} (IC_{50} = 3-6 µM) and PKC_{θ}. Inhibits the PKC_{α}, PKC_{β}, and PKC_{γ} isoforms, but with significantly reduced potency (IC_{50} = 30-42 µM). Has reduced inhibitory activity on PKC, PKC_{η}, and PKC_{ζ} (IC_{50} = 80-100 µM). Also known to inhibit CaM kinase III (IC_{50} = 5.3 µM).	10 mg
Safingol	**559300**	**(L-*threo*-Dihydrosphingosine)** A cell-permeable and reversible *lyso*-sphingolipid protein kinase C (PKC) inhibitor that competitively interacts at the regulatory phorbol binding domain of PKC. Inhibits enzymatic activity and ^3H-phorbol dibutyrate binding of purified rat brain PKC (IC_{50} = 37.5 µM and 31 µM, respectively). Inhibits human PKC_{α}, the major overexpressed isoenzyme in MCF-7 DOXR cells (IC_{50} = 40 µM). Enhances the cytotoxic effect of the chemotherapeutic agent Mitomycin C (MMC; Cat. Nos. 47589 and 475820) in gastric cancer cells by promoting drug-induced apoptosis.	1 mg
Sangivamycin	**559307**	**(7-Deaza-7-carbamoyladenosine; NSC-65346)** A cytotoxic purine nucleoside active against human cytomegalovirus (HCMV). A cell-permeable, reversible, selective, and potent protein kinase C (PKC) inhibitor (IC_{50} = 10 µM). The inhibition is competitive with respect to ATP and non-competitive with respect to histone and lipid cofactors.	1 mg

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

Protein Kinase C (PKC) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Scytonemin, *Lyngbya* sp.	**565715**	**(SCY)** A cell-permeable, dimeric indolo-phenol kinase inhibitor that exhibits anti-proliferative and anti-inflammatory properties. Scytonemin inhibits *polo*-like kinase 1 (Plk1), PKCß1, PKCß2, Cdk1/B, Myt1, and Chk1 (IC_{50} = 2.0, 3.4, 2.7, 3.0, 1.2, and 1.4 µM, respectively) in a dose-dependent manner, exhibiting little activity towards PKA or Tie2 (IC_{50} > 10 µM). Effectively inhibits growth factor- or serum-induced proliferation of cell types implicated in inflammatory response (IC_{50} < 8 µM for HUVEC, NHLF, and Jurkat) without any cytotoxic effect on nonproliferating cells.	1 mg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable, reversible, ATP-competitive and broad spectrum inhibitor of protein kinases. Inhibits protein kinase A (IC_{50} = 7 nM), CaM kinase (IC_{50} = 20 nM), myosin light chain kinase (IC_{50} = 1.3 nM), protein kinase C (IC_{50} = 700 pM), and protein kinase G (IC_{50} = 8.5 nM). Also inhibits platelet aggregation induced by collagen or ADP but has no effect on thrombin-induced platelet aggregation. Induces apoptosis in human malignant glioma cell lines. Arrests normal cells at the G_1 checkpoint. A 1 mM (100 µg/214 µl) solution of Staurosporine (Cat. No.569396) in DMSO is also available.	100 µg 250 µg
Tamoxifen Citrate	**579000**	A potent synthetic anti-estrogenic agent. A cell-permeable and reversible inhibitor of protein kinase C (IC_{50} = 10 µM). Induces apoptosis in human malignant glioma cell lines and inhibits prostate cancer cell growth by induction of p21 protein.	100 mg
Tamoxifen, 4-Hydroxy-, (Z)-	**579002**	**[(Z)-4-Hydroxytamoxifen; 4-OH-TAM]** A cell-permeable, active metabolite of Tamoxifen (Cat. No.579000) that acts as a potent inhibitor of PKC. It is more potent that teh parent compund and inhibits PKC by modifying its catalytic domain.	5 mg
Vitamin E Succinate	**679130**	**(α-Tocopheryl Succinate; VES)** Enhances the immune response and induces cellular differentiation and/or growth inhibition. VES has been shown to modulate adenylate cyclase and cAMP-dependent proteins, inhibit protein kinase C activity, bind to a cellular vitamin E binding protein, suppress c-*myc* and c-H-*ras* oncogene expression, and regulate TGF-ß protein production. Also shown to induce apoptosis in RL cells. Exhibits antioxidant properties.	100 mg

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), which 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 noncontractile 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 to produce tetrahydrobiopterin, a required cofactor for eNOS activation. More recently PKG has also been linked to brown fat cell differentiation and mitochondrial biogenesis.

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AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

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

Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	**[N-(2-Aminoethyl)-5-chloronaphthalene-1-sulfonamide, HCl]** A cell-permeable, reversible, and shorter alkyl chain derivative of W-7 that inhibits casein kinase I (K_i = 80 µM), casein kinase II (K_i = 5.1 µM), myosin light chain kinase (K_i = 7.4 µM), protein kinase A (K_i = 4.3 µM), protein kinase C (K_i = 47 µM), and protein kinase G (K_i = 3.8 µM).	10 mg
Drosophila Antennapedia Homeo-Domain (43-58)	**287895**	**(DT-5; RQIKIWFQNRRMKWKK)** The membrane translocation signal sequence from *Drosophila* Antennapedia homeo-domain (43-58) that is reported to act as an inhibitor of protein kinase G Iα (K_i = 970 nM). Does not exhibit significant inhibition against protein kinase A (PKA) (K_i = 107 µM). May be useful for intracellular delivery of highly charged peptides by covalent attachment.	1 mg
Guanosine 3',5'-cyclic Monophosphorothioate, 8-(4-Choloro- henylthio)-, Rp-Isomer, Triethylammonium Salt	**370677**	**(Rp-8-pCPT-cGMPS, TEA)** A potent, cell-permeable, and metabolically-stable inhibitor of protein kinase G Iα, Iß, and type II. Significantly more lipophilic and membrane-permeable than Rp-cGMPS or Rp-8-Br-cGMPS (Cat. No.370674). Note: 1 µmol = 0.61 mg.	1 µmol
Guanosine 3',5'-cyclic Monophosphorothioate, 8-Bromo-, Rp-Isomer, Sodium Salt	**370674**	**(Rp-8-Br-cGMPS, Na)** A potent, cell-permeable, and metabolically stable inhibitor of protein kinase G (PKG; K_i = 4 µM). Acts as a cyclic nucleotide-gated channel agonist (EC_{50} = 173.5 µM). Significantly more lipophilic and membrane-permeable than cGMP or Rp-cGMPS. Resistant to mammalian cyclic nucleotide-dependent phosphodiesterases. Note: 5 µmol = 2.31 mg.	5 µmol
Guanosine 3',5'-cyclic Monophosphorothioate, b-Phenyl-1, N2-etheno- 8-bromo-, Rp-Isomer, Sodium Salt	**370679**	**(Rp-8-Br-PET-cGMPS, Na)** A metabolically-stable, competitive inhibitor of protein kinase G types 1α and 1ß (K_i = 30 nM). Blocks cGMP-gated retinal type ion channels (IC_{50} = 25 µM) and 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). Note: 1 µmol = 0.56 mg.	1 µmol
H-7, Dihydrochloride	**371955**	**[1-(5-Isoquinolinesulfonyl)-2-methylpiperazine, 2HCl]** A broad-based, cell-permeable, reversible, ATP-competitive serine/threonine kinase inhibitor. Inhibits protein kinase A (K_i = 3.0 µM), myosin light chain kinase (K_i = 97 µM), protein kinase C (K_i = 6.0 µM), and protein kinase G (K_i = 5.8 µM). Induces apoptotic DNA fragmentation and cell death in HL-60 human promyelocytic leukemia cells. Also inhibits telomerase activity in quercetin-, H-89-, or herbimycin A-treated NPC-076 cells.	1 mg 5 mg
H-9, Dihydrochloride	**371961**	**[N-(2-Aminoethyl)-5-isoquinolinesulfonamide, 2HCl]** Closely resembles H-8 in chemical structure and inhibitory potency. A cell-permeable, reversible, and ATP-competitive inhibitor of protein kinase A (K_i = 1.9 µM), protein kinase C (K_i = 18 µM), and protein kinase G (K_i = 870 nM). Useful as a ligand for separation and purification of these enzymes.	1 mg

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

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

Product	Cat. No.	Comments	Size
HA 1004, Dihydrochloride	**371964**	**[N-(2-Guanidinoethyl)-5-isoquinolinesulfonamide, 2HCl]** A cell-permeable, reversible, and ATP-competetive inhibitor of protein kinase A (K_i = 2.3 µM), CaM kinase II (K_i = 13 µM), myosin light chain kinase (K_i = 150 µM), protein kinase C (K_i = 40 µM), and protein kinase G (K_i = 1.3 µM). An intracellular Ca^{2+} antagonist with no effect on cardiac function. Causes selective pulmonary vasodilation during pulmonary hypertension.	1 mg
HA 1077, Dihydrochloride	**371970**	**[Fasudil; (5-Isoquinolinesulfonyl)homopiperazine, 2HCl]** A cell-permeable, reversible, and ATP-competitive Ca^{2+} antagonist with anti-vasospastic properties. Inhibits protein kinase A (K_i = 1.6 µM), protein kinase G (K_i = 1.6 µM), and myosin light chain kinase (K_i = 36 µM). Also reported to potently inhibit Rho-associated kinase (ROCK; IC_{50} = 10.7 µM). Prevents apoptosis and enhances the survival and cloning efficiency of dissociated hES cells without affecting their pluripotency.	1 mg
InSolution™K-252a, *Nocardiopsis* sp.	**420297**	A 1 mM (100 µg/214 µl) solution of K-252a (Cat. No. 420298) in anhydrous DMSO.	100 µg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable, reversible, and ATP-competitive inhibitor against multiple protein kinases, including, but not limited to, CaM kinase II (K_i = 1.8 nM), myosin light chain kinase (K_i = 20 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), protein kinase G (K_i = 20 nM), NGF receptor $gp140^{trk}$ (IC_{50} = 3 nM), its transforming *trk* oncogenes, and the related neurotrophin receptors $gp145^{trkB}$ and $gp145^{trkC}$. Reported to induce apoptosis and cell cycle arrest by decreasing Cdk1 and Cdc25c activity in T98G cells and inhibit Flt3 phosphorylation in Flt3/Itd-BaF3 cells (IC_{50} <50 nM). Also available as a premade 1 mM (100 µg/214 µl) solution in DMSO (Cat. No.420297).	100 µg
K-252b, *Nocardiopsis* sp.	**420319**	A cell-permeable, reversible, ATP-competitive, and non-selective inhibitor of protein kinase C (K_i = 20 nM), myosin light chain kinase (K_i = 147 nM), protein kinase A (K_i = 90 nM), and protein kinase G (K_i = 100 nM).	50 µg 100 µg
KT5823	**420321**	Highly specific, cell-permeable, reversible, and ATP-competitive inhibitor of protein kinase G (K_i = 234 nM).	50 µg 100 µg
PknG Inhibitor	**370653**	**[AX20017; Mycobacterial Protein Kinase G Inhibitor; 2-(Cyclopropanecarbonylamino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide]** A cell-permeable tetrahydrobenzothiophene compound that acts as a highly specific and ATP-binding site-targeting inhibitor against mycobacterial protein kinase G (PknG; IC_{50} = 390 nM), while exhibiting much reduced or no activity against 8 other mycobacterial and 25 other human kinases, including PKCα, the mammalian kinase most closely related to PknG. AX20017 is shown to completely inactivate PknG-mediated blockage of lysosomal transfer and degradation of *M. bovis* BCG in macrophages at concentrations (10µM or higher) that does not otherwise affect the growth of BCG outside its infected host.	10 mg
Protein Kinase G Iα Inhibitor, Cell-Permeable	**370655**	**(DT-3; cGMP-dependent Protein Kinase Iα Inhibitor, Cell-permeable; cGPK Iα Inhibitor, Cell-permeable; RQIKIWFQNRRMKWKKLRKKKKKH)** A highly potent, reversible, and substrate competitive membrane-permeable *Drosophila* Antennapedia homeodomain fused-peptide that selectively inhibits protein kinase G Iα (K_i = 25 nM). Shown to efficiently translocate into arterial smooth muscle cells and inhibit NO-induced vasodilation (ED_{50} = 47 µM). Inhibits protein kinase A at much higher concentrations (K_i = 493 µM). The carrier peptide is also available under Cat. no. 287895.	1 mg
Protein Kinase G Inhibitor	**370654**	**(PKG Inhibitor; RKRARKE)** A more specific, reversible, and substrate competitive inhibitor of protein kinase G (K_i = 86 µM) relative to protein kinase A (K_i = 550 µM). Sequence corresponds to a non-phosphorylatable analog (Ser^{32} to Ala^{32}) of histone H2B (amino acids 29-35).	1 mg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable, reversible, ATP-competitive and broad spectrum inhibitor of protein kinases. Inhibits protein kinase A (IC_{50} = 7 nM), CaM kinase (IC_{50} = 20 nM), myosin light chain kinase (IC_{50} = 1.3 nM), protein kinase C (IC_{50} = 700 pM), and protein kinase G (IC_{50} = 8.5 nM). Also inhibits platelet aggregation induced by collagen or ADP but has no effect on thrombin-induced platelet aggregation. Induces apoptosis in human malignant glioma cell lines. Arrests normal cells at the G_1 checkpoint. A 1 mM (100 µg/214 µl) solution of Staurosporine (Cat. No.569396) in DMSO is also available.	100 µg 250 µg

AGC KINASE INHIBITORS (PKA, PKC, AND PKG)

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

Product	Cat. No.	Comments	Size
Staurosporine, N-Benzoyl	**539648**	**(CGP 41 251; N-Benzoylstaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derivative that displays antitumor properties. Acts as a broad-spectrum, reversible, and ATP-competitive inhibitor of PKC (α, ß and γ), PDGFRß, VEGFR2, Syk, PKCη, PKCδ, Flk-1, Flt3, Cdk1/B, PKA, c-Kit, c-Fgr, c-Src, VEGFR1, and EGFR (IC_{50} = 22 nM, 50 nM, 86 nM, 95 nM, 160 nM, 330 nM, 390 nM, 528 nM, 570 nM, 570 nM, 600 nM, 790 nM, 800 nM, 912 nM, and 1.0 µM, respectively). At higher concentrations, also inhibits Ins-R and IGF-1R (IC_{50} = 10 &tmicroM). Shown to potently inhibit the proliferation of Ba/F3 cells expressing constitutively active Flt3 (IC_{50} < 10 nM).	1 mg
UCN-01	**539644**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp; 7-Hydroxystaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derived anticancer agent that reversibly and ATP-competitively inhibits several protein kinases (IC_{50} = 29 nM, 34 nM, 30 nM, 590 nM and 530 nM for PKCα, PKCß, PKCγ, PKCδ and PKC; IC_{50} = 7 nM, 27 nM, 50 nM, 50 nM, 150 nM and 1.04 µM for Chk1, Cdc25C-associated protein kinase 1, Cdk1, PAK4, Cdk5/p25 and Chk2; IC_{50} = 33 nM, 50 nM, 95 nM, 500 nM, 500 nM and 1.0 µM for PDK1, lck, MAPKAP kinase-2, Akt, GSK-3ß and PKA, respectively). At higher concentrations (> 15 µM), affects the activities of Src, PIM-1, CKII, DNA-PK, ErK1, ILK-1 and MAPKK1). Reported to suppress thymidylate synthase expression, induce apoptosis with caspase activation, and sensitize tumor cells to a range of DNA-damaging agents.	500 µg
UCN-02	**539645**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp.; 7-epi-Hydroxystaurosporine)** A cell-permeable ATP-competitive PKC inhibitor that exhibits decreased potency and selectivity towards calcium-dependent isoforms (IC_{50} = 0.53, 0.7, 0.39, 2.83, and 1.23 µM for PKCα, PKCß, PKCγ, PKCδ, and PKC, respectively) when compared with its stereoisomer UCN-01 (Cat. No.539644). Does not inhibit PKCζ even at concentrations as high as 10 µM.	500 µg

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 identification of Akt as a key regulator of cellular survival has significant implications for oncogenesis. A number of oncogenes and tumor suppressor genes that function upstream of Akt influence cancer progression by regulating Akt. 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 inducing expression of 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

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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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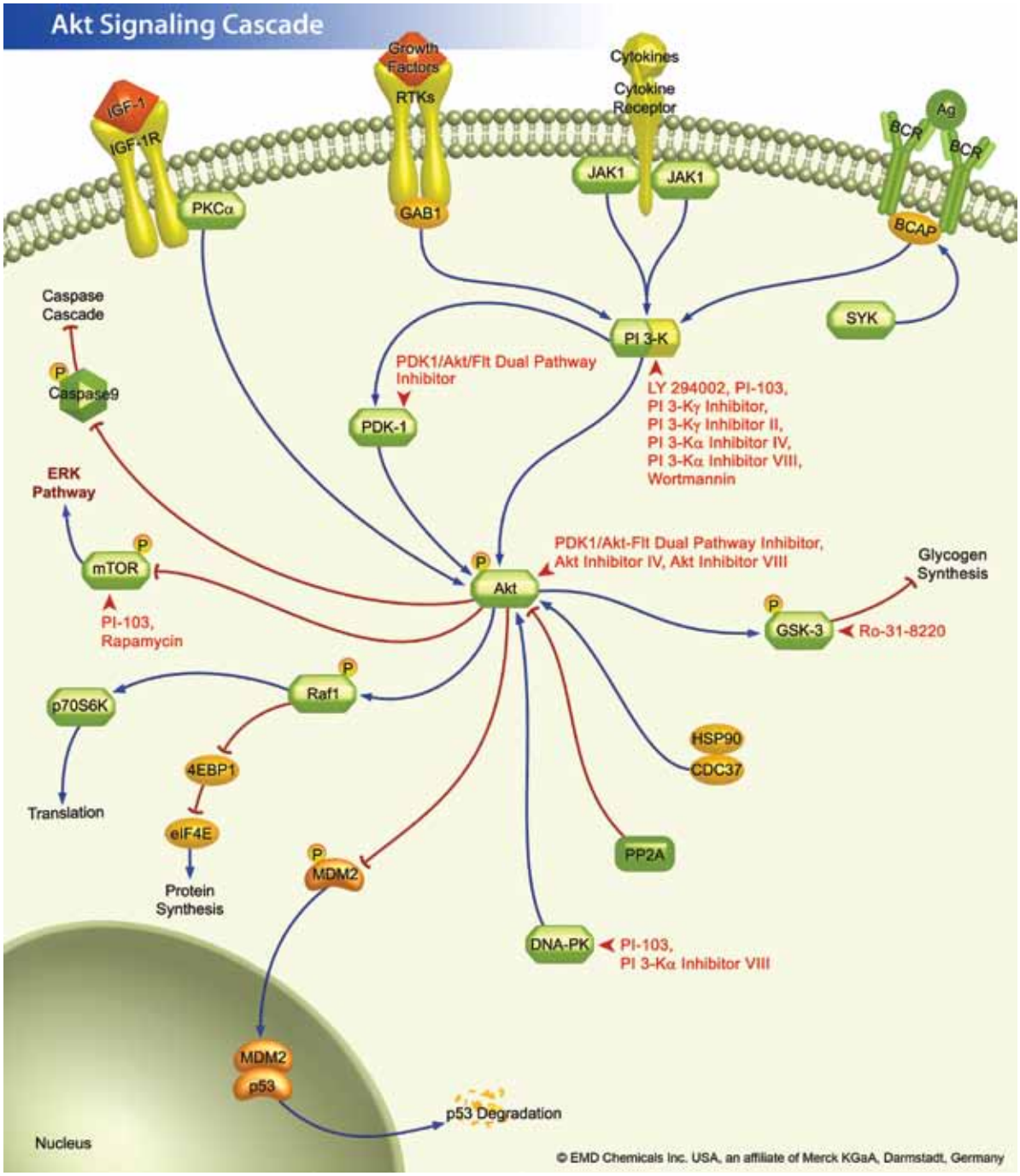
Highlighted below are inhibitors included in InhibitorSelect™ Akt/PI 3-K/mTOR Signaling Pathway Inhibitor Panel (Cat. No. 124031). See page 17, 19 or 203 for details.



AKT, PI 3-KINASE, mTOR INHIBITORS

Akt (Protein Kinase B) Inhibitors

Product	Cat. No.	Comments	Size
Akt Inhibitor	**124005**	**[1L-6-Hydroxymethyl-*chiro*-inositol 2-(R)-2-O-methyl-3-O-octadecylcarbonate]** A cell permeable, reversible, and substrate competitive phosphatidylinositol ether analog that potently and selectively inhibits Akt (PKB) (IC_{50} of 5.0 µM). Moderately inhibits PI 3-K activity (IC_{50} = 83.0 µM). Also inhibits the growth of various cancer cell lines with IC_{50} values in the 1 - 10 µM range.	1 mg
Akt Inhibitor II	**124008**	**(SH-5)** A cell permeable, reversible, and substrate competitive phosphatidylinositol analog that inhibits the activation of Akt and select downstream substrates without decreasing phosphorylation of PDK-1 or other kinases downstream of Ras, such as MAPK. Also acts as a potent inducer of apoptosis and selectively kills a variety of cancer cell lines that contain high levels of active Akt. When used at a concentration of 10 µM, it is reported to activate p38α/SAPK2α MAP kinase. At 10 µM it will also inhibit ~50% of PKA activity.	1 mg
Akt Inhibitor III	**124009**	**(SH-6)** A cell permeable, reversible, and substrate competitive phosphatidylinositol analog that inhibits the activation of Akt and select downstream substrates without decreasing phosphorylation of PDK-1 or other kinases downstream of Ras, such as MAPK. Also acts as a potent inducer of apoptosis and selectively kills a variety of cancer cell lines that contain high levels of active Akt. When used at a concentration of 10 µM, it is reported to activate p38α/SAPK2α MAP kinase. At 10 µM it will also inhibit PKA activity.	1 mg
Akt Inhibitor IV	**124011**	A cell permeable and reversible benzimidazole compound that inhibits Akt phosphorylation/ activation by targeting the ATP binding site of a kinase upstream of Akt, but downstream of PI 3-K. Shown to block Akt-mediated FOXO1a nuclear export (IC_{50} = 625 nM) and cell proliferation (IC_{50} < 1.25 µM) in 786-O cells. Unlike phosphatidylinositol analog-based Akt inhibitors (Cat. Nos. 124005, 124008, 124009), this inhibitor does not affect PI3K. A 10 mM (1 mg/163 µl) solution of Akt Inhibitor IV (Cat. No.124015) in DMSO is also available.	1 mg 5 mg
InSolution™Akt Inhibitor IV	**124015**	A 10 mM (1 mg/163 µl) solution of Akt Inhibitor IV (Cat. No. 124011) in DMSO.	1 mg
Akt Inhibitor IX, API-59CJ-OMe	**124019**	A cell-permeable ellipticine compound that potently and selectively induces apoptosis in human endometrial cancer cells (RL95-2 and Ishikawa) that exhibit elevated Akt activity (effective concentration = 12-24 µM), but not on cells with low Akt activity. Directly affects the activity by Akt, but not the level of cellular phosphorylation of Akt, ERK1/2, JNK1/2, PDK1, PKC isoforms, or serum and glucocorticoid-inducible kinase (SGK).	5 mg
Akt Inhibitor V, Triciribine	**124012**	**(Akt/PKB Signaling Inhibitor-2; API-2; NSC 154020; TCN)** A cell-permeable and reversible tricyclic nucleoside that selectively inhibits the cellular phosphorylation/activation of Akt1/2/3. It does not inhibit known upstream activators of Akt, i.e. PI3K or PDK. Exhibits little effect towards cellular signaling pathways mediated by PKC, PKA, SGK, Stat3, p38, ERK1/2, or JNK. Shown to preferentially induce apoptosis and growth arrest in cancer cells with aberrant Akt activity both *in vitro* (≥ 60% in cell proliferation at 20 µM) and *in vivo* (≥ 80% inhibition in tumor growth in mice at 1 mg/kg/day, i.p.).	1 mg
Akt Inhibitor VI, Akt-in	**124013**	**(H-AVTDHPDRLWAWEKF-OH; $TCL1_{10-24}$)** A reversible 15-mer peptide derived from proto-oncogene TCL1 (amino acids 10-24) that acts as a specific inhibitor of Akt. Shown to bind to Akt-PH domain (K_d ~18 µM) and interfere with the Akt-phosphoinositide interaction, thus hindering membrane translocation from the cytosol and downstream biological responses.	2 mg
Akt Inhibitor VII, TAT-Akt-in	**124014**	**(H-YGRKKRRQRRR-AVTDHPDRLWAWEKF-OH; TAT-$TCL1_{10-24}$)** A cell-permeable and reversible version of the Akt Inhibitor VI, *Akt-in* (Cat. No.124013) fused with the protein transduction domain TAT that displays antitumor properties. Inhibits the phosphorylation of Akt selectively in HEK 293 and QRsP-11 fibrosarcoma cells stimulated with PDGF (complete inhibition at ~ 50 µM) with minimal inhibition towards PKA, PKC, PDK1, p42/44 MAPK, or p38 MAPK. Shown to prevent the proliferation of T4 cells, and tumor growth in syngeneic C57BL/6 mice.	2 mg
InSolution™Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2	**124017**	A 10 mM (1 mg/181 µl) solution of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No. 124018) in DMSO.	1 mg

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AKT, PI 3-KINASE, mTOR INHIBITORS

Akt (Protein Kinase B) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2	**124018**	**{Akti-1/2; 1,3-Dihydro-1-(1-((4-(6-phenyl-1H-imidazo[4,5-g]quinoxalin-7-yl) phenyl)methyl)-4-piperidinyl)-2H-benzimidazol-2-one}** A cell-permeable and reversible quinoxaline compound that potently and selectively inhibits Akt1/Akt2 activity (IC_{50} = 58 nM, 210 nM, and 2.12 µM for Akt1, Akt2, and Akt3, respectively, in *in vitro* kinase assays). The inhibition appears to be pleckstrin homology (PH) domain-dependent. It does not exhibit any inhibitory effect against PH domain-lacking Akts, or other closely related AGC family kinases, PKA, PKC, and SGK, even at concentrations as high as 50 µM. Overcomes Akt1/Akt2-mediated resistance to chemotherapeutics in tumor cells and is shown to block basal and stimulated phosphorylation/activation of Akt1/Akt2 both in cultured cells *in vitro* and in mice *in vivo*. A 10 mM (1 mg/181 µl) solution of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124017) in DMSO is also available.	1 mg
Akt Inhibitor X	**124020**	A cell-permeable, reversible, and selective inhibitor of the phosphorylation of Akt and its *in vitro* kinase activity (complete inhibition 50 = 2-5 µM), inhibit IGF-I-stimulated nuclear translocation of Akt, and prevent phosphorylation of the downstream targets, mTOR, p70S6 kinase, and S6 ribosomal protein. Unlike Akti1/2 (Cat. No. 124018), the mode of inhibition is not PH domain-dependent.	5 mg
Akt Inhibitor XI	**124028**	**[FPA-124; 3-Formylchromone thiosemicarbazone, Cu(II)Cl_2 Complex]** A cell-permeable copper complex (Cu^{2+}/Cu^{+} redox couple in the range of +0.28 to +0.35 V) that interacts with both the PH and the kinase domains of Akt and potently inhibits its kinase activity (IC_{50} = 100 nM). Inhibits tumor growth both in cultured cells *in vitro* (IC_{50} ranges from 10 to 34 µM) and in mice *in vivo* (25 mg/kg, iv) without any apparent adverse effect to the animals.	5 mg
Akt Inhibitor XII, Isozyme-Selective, Akti-2	**124029**	**[1-((2-(4-((4-(2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl)methyl) phenyl)-3-phenyl-6-quinoxalinyl)carbonyl)-4-methyl-piperazine, 3HCl]** A cell-permeable Akti-1/2- (Cat. No.124018) derived allosteric inhibitor pair (1:1 regioisomeric mixture) with much improved aqueous solubility (10 mg/ml in a pH 7.4 saline) and Akt2 selectivity (IC_{50} = 805 nM for Akt2, >10 µM for Akt1/3, and >50 µM for PKA/PKC/SGK). The inhibition is PH domain-dependent and non-competitive with ATP.	2 mg
Akt Inhibitor XIII, Isozyme-Selective, Akti2-1/2	**124030**	**[N-(2-(Diethylamino)ethyl)-2-(4-((4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl)methyl)phenyl)-3-phenyl-6-quinolinecarboxamide, 3HCl]** A highly cell-permeable and water soluble analog of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018) that acts as a plecktrin homology (PH)-domain dependent, non-ATP competitive and an allosteric inhibitor of Akt1/2 (IC_{50} = 560 nM, 390 nM and 7.8 µM in *in vitro* kinase assay; 526 nM, 730 nM and > 10 µM in LNCaP cells for Akt1, Akt2 and Akt3, respectively) with ~ 80-fold greater selectivity over PKA, PKC and SGK (IC_{50} > 50 µM). One of its potent regioisomers (C7-substituted) is shown to enhance induced caspase-3 activity in several tumor cells.	2 mg
Biligand Kinase Inhibitor	**201110**	**[ARC-902; Adc-Ahx-(D-Arg)6-NH_2]** A cell-permeable adenosine carboxylic acid conjugate of hexa-D-Arginine peptide designed to target both the donor (ATP) and acceptor substrate binding sites of basophilic protein kinases. Shown to strongly inhibit several AGC kinases (by ≥95% at 1 µM), including MSK1, p70 S6K, PKBα/ß, and ROCK II, among a 52 kinase panel.	500 µg
(-)-Deguelin, *Mundulea sericea*	**252740**	A cell-permeable rotenoid compound that displays anti-proliferative properties. Potently inhibits mitochondrial bioenergetics (IC_{50} = 6.9 nM for NADH:ubiquinone oxidoreductase activity in bovine heart ETP) and promotes mitochondrial permeability transition. Blocks phorbol ester-induced ornithine decarboxylase activity in MCF-7 cells (IC_{50} = 11 nM) and induces apoptosis and cell cycle arrest. Selectively blocks Akt activation with minimal effects on MAPK signaling. Also shown to activate AMPK activity and inhibit COX2 expression.	5 mg
InhibitorSelect™ Akt/PI 3-K/mTOR Signaling Pathway Inhibitor Panel	**124031**	A panel of 12 highly potent and selective kinase inhibitors and a negative control useful for the study of Akt/PI 3-K/mTOR signaling pathway. This panel contains the following inhibitors: 1 mg of Akt Inhibitor IV (Cat. No.124011); 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018); 5 mg of LY-294002 (Cat. No.440202); 1 mg of LY 303511 (Cat. No.440203); 5 mg of PDK1/Akt/Flt Dual Pathway Inhibitor (Cat. No.521275); 1 mg of PI-103 (Cat. No.528100); 5 mg of PI 3-Kγ Inhibitor (Cat. No.528106); 5 mg of PI 3-Kγ Inhibitor II (Cat. No.528108); 5 mg of PI 3-Kα Inhibitor IV (Cat. No.528111); 5 mg of PI 3-Kα Inhibitor VIII (Cat. No.528116); 100 µg of Rapamycin (Cat. No.553210); 500 µg of Ro-31-8220 (Cat. No.557520); and 1 mg of Wortmannin (Cat. No.681675). Also provided is 15 ml of anhydrous DMSO. Supplied with a data sheet.	1 ea

AKT, PI 3-KINASE, mTOR INHIBITORS

Akt (Protein Kinase B) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Naltrindole, Hydrochloride	**476880**	**(NTI)** A cell-permeable, δ-selective opioid receptor antagonist (K_i = 0.031, 3.8, and 332.7 nM for δ, μ, and κ, respectively) and an inhibitor of cellular Akt signaling. Decreases the cellular phosphorylation level of PDK1, Akt, FKHR/AFX, GSK-3ß, and inhibits Akt-dependent cell growth in small cell lung cancer (SCLC) cell lines (IC_{50} = 25, 40, and 55 μM in NCI-H69, NCI-H345, and NCI-H510, respectively).	5 mg
PDK1/Akt/Flt Dual Pathway Inhibitor	**521275**	**{6H-Indeno[1,2-e]tetrazolo[1,5-b][1,2,4]triazin-6-one & 10H-Indeno[2,1-e]tetrazolo[1,5-b][1,2,4]triazin-10-one}** A cell-permeable compound that selectively induces apoptosis in AML (Acute Myelogenous Leukemia) with little effect on normal $CD34^+$ AML progenitor cells. Shown to directly inhibit both PDK1 and Akt activities in *in vitro* kinase assays in a dose-dependent manner and block cellular phosphorylation of Akt at both Ser^{473} and Thr^{308}. The dual inhibition nature against both PDK1/Akt and Flt3/PIM signaling pathways allows effective killing of AML cells (Average IC_{50} = 1.05, 1.91, and 0.43 μM for AML with wild-type Flt3, single mutant ITD/D835, and double mutant Flt3-ITD-TDK, respectively) that are otherwise resistant to inhibitors that target only the PDK1/Akt pathway.	5 mg
Rapamycin	**553210**	Anti-fungal and immunosuppressant. Selectively inhibits the phosphorylation and activation of p70 S6 kinase (IC_{50} = 50 pM). Prevents the translational activation of IGF-II. Shown to inhibit later signaling events such as $p110^{Rb}$ phosphorylation, $p34^{cdk1}$ kinase activation, and cyclin A synthesis. Exhibits strong binding to FK-506 binding proteins. Reported to induce apoptosis in a murine B cell line, to inhibit lymphokine-induced cell proliferation at the G_1 phase, and to irreversibly arrest *Saccharomyces cerevisiae* cells in the G_1 phase. A 5 mM (500 μg/109 μl) solution of Rapamycin (Cat. No.553211) in DMSO and a 10 mM (1 mg/109 μl) solution of Rapamycin (Cat. No.553212) in EtOH is also available.	1 mg
InSolution™Rapamycin	**553211**	A 5 mM (500 μg/109 μl) solution of Rapamycin (Cat. No. 553210) in DMSO.	500 μg
InSolution™Rapamycin in EtOH	**553212**	**(Sirolimus)** A 10 mM (1 mg/109 μl) solution of Rapamycin (Cat. No. 553210) in EtOH. Selectively inhibits the phosphorylation and activation of p70 S6 kinase (IC_{50} = 50 pM). Prevents the translational activation of IGF-II. Shown to inhibit later signaling events such as p110Rß phosphorylation, p34cdk1 kinase activation, and cyclin A synthesis. Exhibits strong binding to FK-506 binding proteins. Reported to induce apoptosis in a murine B cell line, to inhibit lymphokine-induced cell proliferation at the G1 phase, and to irreversibly arrest *Saccharomyces cerevisiae* cells in the G1 phase.	1 mg
Serine/Threonine Kinase Inhibitor Set	**539572**	A convenient set that offers several highly selective serine/threonine kinase inhibitors. Set contains 250 μg of protein kinase C inhibitor, Bisindolylmaleimide I (Cat. No.203290); 1 mg of protein kinase A 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 Serine/Threonine Kinase inhibitor, Staurosporine (Cat. No.569397). Supplied with a data sheet.	1 set

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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)P_2 as substrates *in vitro*. The major substrate *in vivo* appears to be PI(4,5)P_2. 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)P_2, and PI(3,4,5)P_3. 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 signaling is crucial to many aspects of cell growth and survival and this pathway is stimulated by many growth factors. Hence, PI 3-kinase activity is tightly regulated in normal cells. Abnormal activity of PI 3-kinase is seen in several forms of cancer. About 30% of solid tumors contain mutations in the catalytic subunit of PI 3-kinase. 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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AKT, PI 3-KINASE, mTOR INHIBITORS

Phosphatidylinositol 3-Kinase (PI 3-kinase) Inhibitors

Product	Cat. No.	Comments	Size
ET-18-OCH_3	**341207**	**(Edelfosine; 1-O-Octadecyl-2-O-methyl-*rac*-glycero-3-phosphorylcholine)** A cell-permeable and reversible cytotoxic agent that shows selective cytocidal activity against neoplastic cells and virally transformed cells. Selectively inhibits phosphatidylinositol-specific phospholipase C (PI-PLC; IC_{50} = 15 µM) but does not inhibit phosphatidylcholine-specific PLC or PLD. Promotes apoptosis in mitogen-activated, but not resting, T lymphocytes in a dose- and time-dependent manner. Also promotes rapid and selective apoptosis in human leukemic cells.	5 mg
InhibitorSelect™ Akt/PI 3-K/mTOR Signaling Pathway Inhibitor Panel	**124031**	A panel of 12 highly potent and selective kinase inhibitors and a negative control useful for the study of Akt/PI 3-K/mTOR signaling pathway. This panel contains the following inhibitors: 1 mg of Akt Inhibitor IV (Cat. No.124011); 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018); 5 mg of LY-294002 (Cat. No.440202); 1 mg of LY 303511 (Cat. No.440203); 5 mg of PDK1/Akt/Flt Dual Pathway Inhibitor (Cat. No.521275); 1 mg of PI-103 (Cat. No.528100); 5 mg of PI 3-Kγ Inhibitor (Cat. No.528106); 5 mg of PI 3-Kγ Inhibitor II (Cat. No.528108); 5 mg of PI 3-Kα Inhibitor IV (Cat. No.528111); 5 mg of PI 3-Kα Inhibitor VIII (Cat. No.528116); 100 µg of Rapamycin (Cat. No.553210); 500 µg of Ro-31-8220 (Cat. No.557520); and 1 mg of Wortmannin (Cat. No.681675). Also provided is 15 ml of anhydrous DMSO. Supplied with a data sheet.	1 ea

AKT, PI 3-KINASE, mTOR INHIBITORS

Phosphatidylinositol 3-Kinase (PI 3-kinase) Inhibitors *continued*

Product	Cat. No.	Comments	Size
LY 294002	**440202**	**[2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one]** A cell-permeable, potent, reversible and specific phosphatidylinositol 3-kinase inhibitor (IC_{50} = 1.4 µM) that acts on the ATP-binding site of the enzyme. Also inhibits nonhomologous DNA end-joining (NHEJ) activity of the 460 kDa phosphatidylinositol 3-like kinase DNA-PKc$_s$, which is the catalytic subunit of DNA-activated protein kinase. Does not affect the activities of EGF receptor kinase, MAP kinase, PKC, PI 4-kinase, S6 kinase, and c-Src even at 50 µM. Blocks the proliferation of cultured rabbit aortic smooth muscle cells without inducing apoptosis. A 10 mM (1 mg/325 µl) solution of LY 294002 (Cat. No.440204) in DMSO is also available.	5 mg
InSolution™LY 294002	**440204**	**[2-(4-Morpholinyl)-8-phenyl-4H-1-benzopyran-4-one]** A 10 mM (1 mg/325 µl) solution of LY 294002 (Cat. No. 440202) in anhydrous DMSO.	1 mg
LY 294002, 4'-NH_2	**440206**	**[PI-828; 2-(4-Morpholinyl)-8-(4-aminophenyl)-4H-1-benzopyrone-4-one]** A cell-permeable LY 294002 (Cat. Nos.440202 &t440204) 4'-amino derivative with enhanced potency against p110α/ß/δ/γ (IC_{50} in nM/-fold increase in potency = 183/2.7-, 98/5.7-, 1227/.5-, and 1967/1.9-, respectively). The molecule has been immobilized on epoxy-containing solid surface via the 4'-amine for binding studies and shown to interact with non-PI3K cellular proteins, such as mTOR, ALDH1, Brd4, GSK3ß, and CKIIα.	5 mg
LY 303511	**440203**	**(2-Piperazinyl-8-phenyl-4H-1-benzopyran-4-one)** A cell-permeable 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 inhibit PI 3-kinase even at a concentration of 100 µM.	1 mg
Myricetin	**476275**	**(3,3',4',5,5',7-Hexahydroxyflavone)** A cell-permeable flavanoid that displays anti-inflammatory, anti-diabetic and anti-cancer properties. Acts as a non-ATP competitive MEK1 inhibitor (IC_{50} i = 9.0 µM, 0.6 µM, 2.6 µM, 1.7 µM, 27.5 µM and 12.1 µM, respectively) and PI 3-Kα and PIM-1 (IC_{50} = 1.8 µM and 0.78 µM). Reported to inhibit the activities of phosphodiesterase 1-4 (IC_{50} 50 a-mediated NF-κB signaling (at 50 µM in ECV304 cells) and insulin-stimulated glucose transport (K_i = ~ 33.5 µM in rat adipocytes). Further, induce apoptosis in HL-60 leukemia cells with an IC_{50} of 43 µM.	25 mg
PI 3-K inhibitor IX, PIK-90	**528117**	**N-(2,3-Dihydro-7,8-dimethoxyimidazo[1,2-c] quinazolin-5-yl)-3-pyridinecarboxamide** A cell-permeable imidazoquinazoline compound that acts as a potent, reversible and ATP-competitive PI 3-K family selective inhibitor (IC_{50} = 11 nM, 13 nM, 18 nM, 47 nM, 58 nM and 64 nM for p110α, DNA-PK, p110γ, PI 3-KC2α, p110δ and PI 3-KC2ß, respectively). Moderately inhibits p110ß, ATM, PI 4-KIIIα and hsVPS34 (IC_{50} = 350 nM, 610 nM, 830 nM and 830 nM, respectively) with minimal inhibition towards a panel of 36-kinases (IC_{50} > 10 µM). Completely prevents insulin-stimulated Akt phosphorylation in 3T3-L1 adipocytes and L6 myotubes at 2.5 µM, and uptake of glucose in adipocytes and in a mouse model (10 mg/ml, i.p.).	5 mg
PI 3-Kα Inhibitor IV	**528111**	**{3-(4-Morpholinothieno[3,2-d]pyrimidin-2-yl)phenol, 2HCl}** A cell-permeable morpholino-thienopyrimidine compound that acts as a potent and isoform-selective inhibitor of PI 3-kinases (IC_{50} = 2 nM, 16 nM, 660 nM, and 220 nM for p110α, p110ß p110γ, and PI 3-K C2ß, respectively) and inhibits non-PI 3-K kinases only at much higher concentrations (IC_{50} ≥3.4 µM for Cdk2/E, KDR, PKA, and PKCα). Shown to inhibit cell proliferation (IC_{50} = 580 nM) and serum-stimulated Akt phosphorylation (IC_{50} <3 µM) in A375 melanoma cells.	5 mg
PI 3-Kα Inhibitor VIII	**528116**	**{N-((1E)-(6-Bromoimidazo[1,2-a]pyridin-3-yl)methylene)-N'-methyl-N"-(2-methyl-5-nitrobenzene)sulfonohydrazide, HCl}** A cell-permeable imidazopyridine compound that acts as a highly potent and ATP-competitive DNA-PK and p110α-selective PI3-K inhibitor (IC_{50} = 0.3, 40, 100, and 850 nM for p110α, p110γ, PI 3-K C2ß, and p110ß, respectively). Shown to effectively block cellular PI3-K/Akt signaling and inhibit tumor growth both *in vitro* (IC_{50} ≤58 nM in MCF7, MCF7 ADR-res, HeLa, A375, and A549 cultures) and in mice *in vivo* (62% inhibition of HeLa xenograft in 2 weeks, 50 mg/kg/day, i.p.).	5 mg
PI 3-Kγ Inhibitor	**528106**	**[5-Quinoxalin-6-ylmethylene-thiazolidine-2,4-dione]** A cell-permeable thiazolidinedione compound that acts as a potent, selective, and ATP-competitive inhibitor of phosphatidylinositol 3-kinase γ (PI 3-Kγ) (K_i = 7.8 nM; IC_{50} = 8 nM, 60 nM, 270 nM, 300 nM for p110-γ, α, ß and δ-isoforms, respectively). Does not affect the activity of a wide panel of kinases, receptors, enzymes, and ion channels even at concentrations as high as 1 µM. Selectively blocks MCP-1-, but not CSF-1-, dependent Akt phosphorylation and chemotaxis in primary *Pik3cg*$^{+/+}$ murine monocytes and in a human monocytic cell line THP-1 (IC_{50} = 181 nM). Also shown to exhibit *in vivo* efficacy in reducing neutrophil chemotaxis in murine peritonitis and arthritis models.	5 mg

AKT, PI 3-KINASE, mTOR INHIBITORS

Phosphatidylinositol 3-Kinase (PI 3-kinase) Inhibitors *continued*

Product	Cat. No.	Comments	Size
PI 3-Kγ Inhibitor II	**528108**	**5-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione** A cell-permeable thiazolidinedione compound that acts as a potent and ATP-competitive inhibitor of PI 3-Kγ (K_i = 180 nM; IC_{50} = 250 nM). Exhibits great selectivity over PI 3-Kα (IC_{50} = 4.5 µM), PI 3-Kß and δ (IC_{50} > 20 µM), and shows little effect towards a large panel of receptors, unrelated enzymes, ion channels, and 38 commonly studied kinases. Shown to block MCP-1-mediated monocyte chemotaxis *in vitro* and exhibit better *in vivo* efficacy than LY294002 (Cat. No. 440202 and 440204) in blocking RANTES- or thioglycollate-induced peritoneal neutrophil recruitment by oral administration in a murine peritonitis model.	5 mg
PI 3-Kγ Inhibitor VII	**528114**	**{AS041164; 5-(Benzo[1,3]dioxol-5-ylmethylene)-thiazolidine-2,4-dione}** A cell-permeable thiazolidinedione compound that acts as a potent, ATP-competitive, and isoform-selctive PI 3-K inhibitor (IC_{50} = 0.07, 0.24, 1.45, and 1.70 µM for the γ, α, ß, and δ isoform, respectively) with little or no activity against a panel of 38 other commonly studied kinases (50 = 27.35 mg/kg, p.o.) in blocking rhRNATES-induced neutrophil peritoneal recruitment in mice *in vivo*. Also reported to exhibit significant *in vivo* prophylactic efficacy against carrageenan-induced tissue swelling in a rat paw edema model (100 mg/kg, p.o.).	5 mg
PI 3-Kγ/CKII Inhibitor	**528112**	**[(5-(4-Fluoro-2-hydroxyphenyl)furan-2-ylmethylene)thiazolidine-2,4-dione]** A cell-permeable furanyl-thiazolidinedione compound that acts as a potent, ATP-competitive inhibitor of PI 3-Kγ and CKII (IC_{50} = 20 nM). It inhibits other PI 3-K isotypes (IC_{50} = 0.94, 20, and 20 µM for α, ß, δ, respectively) and MKK7ß (IC_{50} >10 µM) only at much higher concentrations and exhibits little activity against 77 other commonly studied kinases even at concentrations as high as 10 µM. Shown to inhibit stimulated Akt phosphorylation in cells *in vitro* and offer blockage of thioglycollate-induced neutrophil recruitment in a murine peritonitis model *in vivo*.	5 mg
PI 3-Kß Inhibitor VI, TGX-221	**528113**	**{(±)-7-Methyl-2-(morpholin-4-yl)-9-(1-phenylaminoethyl)-pyrido[1,2-a]-pyrimidin-4-one}** A cell-permeable morpholino-pyrimidinone compound that acts as a reversible, ATP-competitive, selective, and highly potent inhibitor of PI 3-Kß (IC_{50} = 0.005, 0.1, 5, and ≥3.5 µM for -ß, -δ, -α and -γ isoforms, respectively) with little activity against a panel of 15 commonly studied protein kinases even at concentrations as high as 10.0 µM. An excellent tool for studying p110ß-dependent responses both in cells *in vitro* and in animals *in vivo*.	1 mg
PI-103	**528100**	**{3-(4-(4-Morpholinyl)pyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl)phenol}** A cell-permeable pyridinylfuranopyrimidine compound that acts as a potent and ATP-competitive inhibitor of DNA-PK, PI3-K, and mTOR (IC_{50} = 2, 8, 88, 48, 150, 26, 20, and 83 nM for DNA-PK, p110α, p110ß, p110δ, p110γ, PI3-KC2ß, mTORC1, and mTORC2, respectively). It inhibits ATR and ATM only at much higher concentrations (IC_{50} = 850 and 920 nM, respectively) and exhibits little activity towards a panel of more than 40 other kinases even at concentrations as high as 10 µM. Shown to effectively block PI3-K/Akt signaling and cell proliferation in glioma cell lines both *in vitro* and *in vivo*. A 10 mM (2 mg/574 µl) solution of PI-103 (Cat. No.528101) in DMSO is also available.	1mg 5 mg
InSolution™PI-103	**528101**	A 10 mM (2 mg/574 µl) solution of PI-103 (Cat. No. 528100) in DMSO.	2 mg
PIKfyve Inhibitor	**524611**	**{PtdIns3P 5-Klnase Inhibitor; 6-Amino-N-(3-(4-(4-morpholinyl) pyrido[3'2':4,5]furo[3,2-d]pyrimidin-2-yl)phenyl)-3-pyridine carboxamide}** A cell-permeable pyridofuropyrimidine compound that selectively inhibits mammalian type III PtdInsP kinase (IC_{50} = 33 nM and >5 µM using murine PIKfyve and yeast Fab1, respectively), while exhibiting much reduced activity against p110α (IC_{50} = 3.3 µM) and little activity against type IIγ PtdInsP kinase even at concentrations as high as 10 µM. Shown to block serum-induced PtdIns(3,5)P_2 production in NIH3T3 cells (80% inhibition at 800 nM) and disrupt cellular endosomal transport in a reversible manner.	5 mg
Quercetin, Dihydrate	**551600**	**(3,3',4',5,7-Pentahydroxyflavone)** A cell-permeable and reversible inhibitor of PIM1 kinase (IC_{50} = 43 nM), PI 3-K (IC_{50} = 3.8 µM) and phospholipase A_2 (IC_{50} = 2 µM). Also inhibits mitochondrial ATPase, phosphodiesterases, and protein kinase C. Induces apoptosis in K562, Molt-4, Raji, and MCAS tumor cell lines. Reported to activate sirtuins and promote the survival of eukaryotic cells.	100 mg
InSolution™Rapamycin in EtOH	**553212**	**(Sirolimus)** A 10 mM (1 mg/109 µl) solution of Rapamycin (Cat. No. 553210) in EtOH. Selectively inhibits the phosphorylation and activation of p70 S6 kinase (IC_{50} = 50 pM). Prevents the translational activation of IGF-II. Shown to inhibit later signaling events such as p110Rß phosphorylation, p34cdk1 kinase activation, and cyclin A synthesis. Exhibits strong binding to FK-506 binding proteins. Reported to induce apoptosis in a murine B cell line, to inhibit lymphokine-induced cell proliferation at the G1 phase, and to irreversibly arrest *Saccharomyces cerevisiae* cells in the G1 phase.	1 mg

AKT, PI 3-KINASE, mTOR INHIBITORS

Phosphatidylinositol 3-Kinase (PI 3-kinase) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Wortmannin	**681675**	**(KY 12420)** A cell-permeable, fungal metabolite that acts as a potent, selective, and irreversible inhibitor of phosphatidylinositol 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. Preincubation of fibroblasts with wortmannin abolishes PDGF-mediated Ins(3,4,5)P_3 formation (IC_{50} = 5 nM). Also blocks the metabolic effects of insulin in isolated rat adipocytes without affecting the insulin receptor tyrosine kinase activity. Inhibits MAP kinase activation induced by platelet activating factor in guinea pig neutrophils (200 - 300 nM). Also inhibits other kinases such as myosin light chain kinase (IC_{50} = 200 nM) and PI 4-kinase at concentrations higher than that required for inhibition of PI 3-kinase. Also blocks phospholipase D. A 10 mM (1 mg/233 µl) solution of Wortmannin (Cat. No.681676) in DMSO is also available.	1 mg
InSolution™Wortmannin	**681676**	A 10 mM (1 mg/233 µl) solution of Wortmannin (Cat. No. 681675) in DMSO.	1 mg

JAK/STAT Signaling

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway play an important role in cell proliferation, cell differentiation, cell migration, and cell death. It is the principal signaling mechanism for a variety of cytokines and growth factors. Constitutive activation or dysregulation of JAK/STAT signaling can result in inflammatory disease, erythrocytosis, gigantism, and leukemia.

In the JAK/STAT signaling scheme, ligand binding to cytokine receptors induces dimerization of their receptor subunits. They may either form homodimers, as in case of erythropoietin, or heterodimers as in case of interferons and interleukins. Following ligand binding, the cytoplasmic domains of two receptor subunits associate with JAK tyrosine kinases. In mammals, the JAK family is composed of four members: JAK1, JAK2, JAK 3, and Tyk2. Ligand binding brings the two JAKs into close proximity, allowing their transphosphorylation. The activated JAKs can then phosphorylate STATs. In mammalian cells seven different STATs been recognized. They contain a conserved tyrosine residue near the C-terminus, which is phosphorylated by JAKs. This tyrosine phosphorylation allows the dimerization of STATs by interacting with a conserved SH2 domain. In their latent form STATs are located in the cytoplasm and upon phosphorylation they are transported into the nucleus by an importin a-5 dependent mechanism. In the nucleus, dimerized STATs bind to specific regulatory sequences to activate or repress transcription of target genes.

JAK/STAT signaling is negatively regulated by three different mechanisms. They include suppressors of cytokine signaling (SOCS), protein inhibitors of activated stats (PIAS) and protein tyrosine phosphatases (PTPs). SOCS proteins contain an SH2 domain and a SOCS box at their C-terminus. They also contain a small kinase inhibitory domain located N-terminal to the SH2 domain. Activated STATs are reported to stimulate transcription of the SOCS genes and the resulting SOCS proteins bind to phosphorylated JAKs and block their activity. The SOCS can also bind to phosphotyrosines residues on the receptors and block the recruitment of STATs to these receptors. The PIAS protein family consists of five members: PIAS1, PIAS3, PIASxa, PIASxb, and PIASy. They bind to activated STAT dimers and prevent their DNA binding. They contain a Zn-binding RING-finger domain in their central domain, a well-conserved SAP (SAF-A/Acinus/PIAS) domain at the N-terminus, and a less-well-conserved carboxyl domain. SHP-1, a tyrosine phosphatase can also regulate JAK/STAT signaling by dephosphorylating JAK. Here, the SH2 domains of SHP-1 bind phosphorylated JAK and/or phosphorylated receptors to block JAK/STAT signaling.

JAK/STAT signaling pathways is also involved in cross talk between the receptor tyrosine kinase/ Ras/MAPK pathway at multiple levels. Activated JAKs can phosphorylate tyrosines on their associated receptors, which serve as docking sites for SH2-containing adapter proteins, such as SHP-2 and Shc, from other signaling pathways. JAK is also reported to phosphorylate insulin receptor substrate (IRS) and p85, which results in the activation of the phosphoinositide 3-kinase (PI 3-K) pathway.

JAK/STAT pathway is reported to play an important role in the establishment of cell fate. For example, IL-12 promotes differentiation of CD4+ T cells to Th1 cells by activating STAT4, and *stat4* knockout mice fail to respond to IL-12 and produce only Th2 cells. On the other hand IL-4 activates STAT6 and promotes differentiation of CD4+ T cells to Th2

cells. JAK/STAT pathway is also involved in hematopoeitic development. Targeting of *Jak2* gene is shown to result in embryonic lethality in mice due to failure of erythropoiesis. In addition, JAK/STAT pathways have been reported to be constitutively active in several forms of human cancers.

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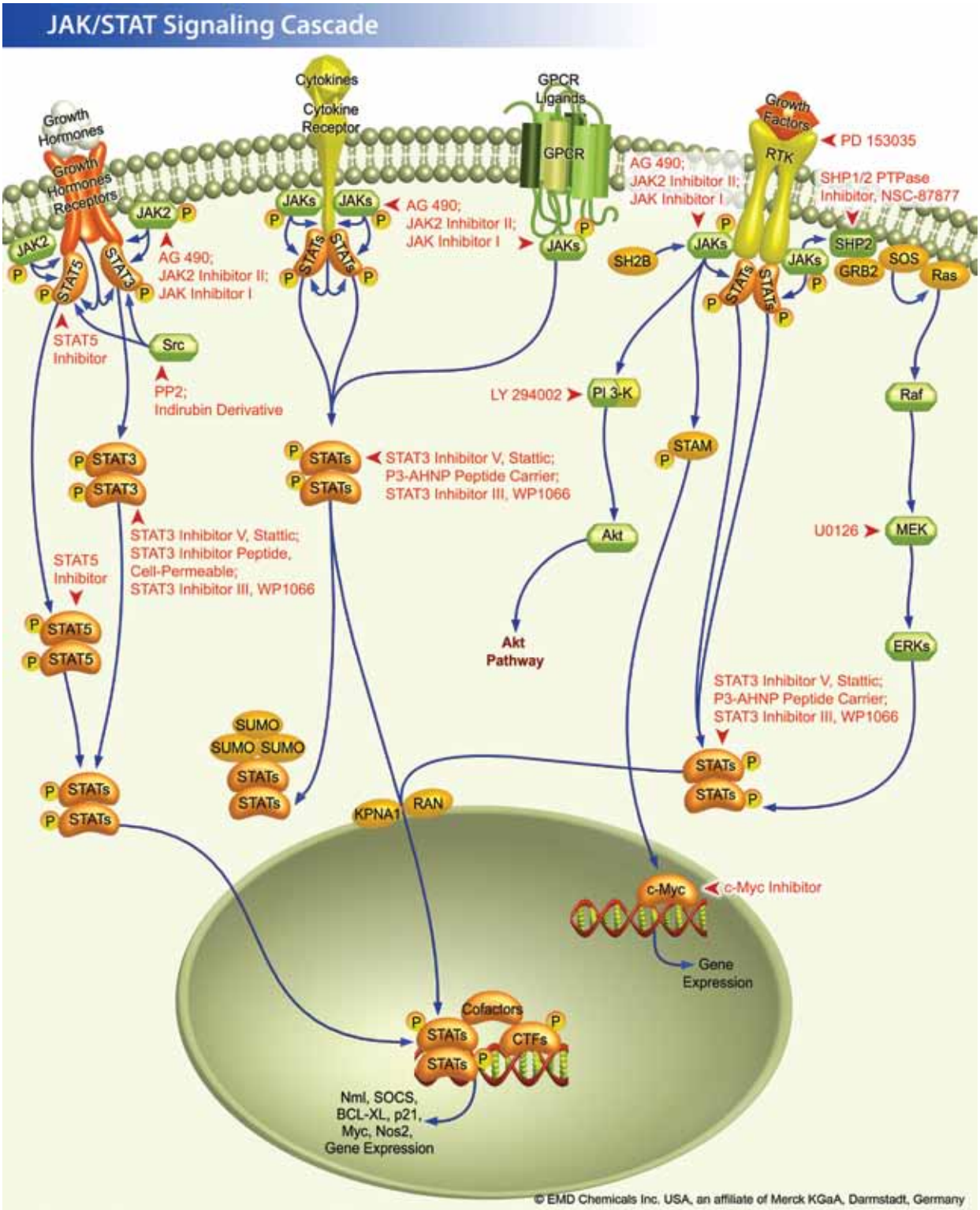
Highlighted below are inhibitors included in InhibitorSelect™ JAK/STAT Signaling Pathway Inhibitor Panel (Cat. No. 420138). See page 204 for details.



JAK/STAT INHIBITORS

JAK Inhibitors

Product	Cat. No.	Comments	Size
JAK2 Inhibitor III	**573098**	**[SD-1029; NSC 371488; 9-(3,4-Dichlorophenyl)-2,7-bis(dimethylaminomethyl)-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione, 2HBr]** A cell-permeable xanthenedione compound that acts as a JAK2-selective inhibitor. It exhibits much less effect on the cellular phosphorylation levels of Jak1 and Src and shows no significant inhibition towards a panel of 49 other protein kinases in cell-free kinase assays at a concentration of 10 µM. Effectively inhibits cell proliferation in JAK-activated BA/F3 cell lines as well as phosphorylation and nuclear translocation of cellular Stat3.	10mg
JAK2 Inhibitor IV	**420139**	**[3-Amino-5-(N-tert-butylsulfonamido-4-phenyl)-indazole]** An aminoindazole compound that potently inhibits the activity of both the wild-type JAK2 and the constitutively active V617F mutant (IC_{50} = 78 and 206 nM, respectively) frequently found in patients with clonal polycythemia vera, essential thrombocytosis, and chronic idiopathic myelofibrosis, while exhibiting much reduced activity against JAK3 (IC_{50} = 2.93 µM).	5mg
JAK2 Inhibitor V, Z3	**420141**	**2-Methyl-1-phenyl-4-pyridin-2-yl-2-(2-pyridin-2-ylethyl)butan-1-one** A cell-permeable pyridinylbutanone compound that inhibits cellular autophosphorylation of both the wild-type Jak2 and the constitutively active V167F mutant (IC_{50} = 15 & 28 µM, respectively, with WT- & V617F-transfected BSC-40 cells), while exhiting no effect against cellular Tyk2 autophosphorylation in COS cells or c-Src kinase in cell-free kinase assays. Z3 suppresses the Jak2-V167F-dependent proliferation of the erythroleukemia cell line HEL by blocking the G1-S transition and is shown to effectively reduce the cytokine-stimulated growth of both Jak2-V617F-positive and Jak2-F537I-positive primary hematopoietic progenitor cells from myeloproliferative disorder patients.	10 mg
JAK3 Inhibitor, Negative Control	**420112**	**4-Phenylamino-6,7-dimethoxyquinazoline, HCl** A useful negative control for JAK3 inhibitors (Cat. Nos. 420101, 420104, and 420106; IC_{50} > 300 µM).	500 µg 1 mg

JAK/STAT INHIBITORS

STAT Inhibitors

Product	Cat. No.	Comments	Size
Cryptotanshinone	**233630**	Cryptotanshinone, a cell-permeable diterpene quinone and naturally occurring herbal constituent of *Salvia miltiorrhiza* Bunge (Danshen), is shown to inhibit the constitutive STAT3 Tyr^{705} phosphorylation in DU145 prostate cancer cells (>90% inhibition in 1 h at 7 µM) independent of the IL-6/JAK/STAT3 signaling pathway, resulting in a blockage of STAT3 dimerization, nuclear translocation, and STAT3-dependent transcription activity (by ~80% in 24 h at 7 µM). Cryptotanshinone is also reported to deplete cellular ATP level (by 75% in 12 h at 20 µM in C2C12 myotubes), resulting in an indirect activation of cellular AMPK pathways and an enhancement of insulin-stimulated cellular glucose uptake in C2C12 myotubes and 3T3-L1 adipocytes (by ~1.3- and 1.9-fold, respectively). Cryptotanshinone is demonstrated to be an orally active hypoglycemic agent in ob/ob mice, db/db mice, and ZDF rats *in vivo* (600 mg/kg/day).	10 mg
Nifuroxazide	**481984**	**(5-Nitro-2-furaldehyde-p-hydroxybenzoylhydrazone)** A cell-permeable and orally available nitrofuran-based antidiarrheal agent that effectively suppresses the activation of cellular STAT1/3/5 transcription activity (IC_{50} = 3 µM against IL-6-induced STAT3 activation in U3A cells), while exhibiting little effect against TNF-α-induced $NF-_{\kappa}B$ activation in 293 cells. Shown to inhibit cellular tyrosine phosphorylations of JAK2/TYK2/STAT3 (IC_{50} = 10 µM against tyr705 of STAT3 in U266 cells), but not those of Akt/EGFR/JAK1/MAPK/Src or the ser727 phosphorylation of STAT3.	500 mg
STAT3 Inhibitor III, WP1066	**573097**	A cell-permeable AG 490 (Cat. No.658401) tyrphostin analog that acts as an effective STAT3 pathway inhibitor and a much more potent antitumor agent than AG 490 in inhibiting malignant glioma growth both in cultures *in vitro* (IC_{50} = 5.6 and 3.7 µM in a viability assay using U87-MG and U373-MG, respectively; no inhibition against nontumor NHA at 10 µM) and in mice *in vivo*. Shown to cross blood-brain barrier in mice *in vivo*.	10 mg
STAT3 Inhibitor Peptide	**573095**	**Ac-PpYLKTK-OH** A Stat3-SH2 domain binding phosphopeptide that acts as a selective inhibitor of Stat3 (signal transducers and activators of transcription 3) signaling with a DB_{50} of 235 µM (concentration of peptide at which DNA-binding activity is inhibited by 50%). Significantly lowers the DNA-binding activity of Stat3 by forming an inactive Stat3:peptide complex and reduces the levels of active Stat3:Stat3 dimers that can bind DNA. Displays greater affinity for Stat3, and to a lesser extent Stat1, over Stat5.	1 mg

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JAK/STAT INHIBITORS

STAT Inhibitors *continued*

Product	Cat. No.	Comments	Size
STAT3 Inhibitor Peptide II, ErbB2-Selective, Cell-Permeable	**573092**	**(P3-AHNP-STAT3BP; H-YGRKKRRQR-G-FCDGFYACYKDV-PpYL-OH, Cyclic)** The SH2 domain-binding motif- (Cat. No.573095) derived STAT3 inhibiting sequence, PpYL (STAT3BP), is conjugated with a cell-permeant carrier sequence P3-AHNP (Cat. No.573094), to allow its preferential delivery to ErbB2 high-expressing cells for STAT3 inhibition. P3-AHNP-STAT3BP has been shown to selectively inhibit the growth of ErbB2-overexpressing cancer cells both *in vitro* and *in vivo*.	2 mg
STAT3 Inhibitor Peptide, Cell-Permeable	**573096**	**(PpYLKTK-mts)** A cell-permeable analog of the Stat3-SH2 domain-binding phosphopeptide (Cat. No.573095) that contains a C-terminal mts (membrane translocating sequence) and acts as a highly selective, potent blocker of Stat3 activation. Also suppresses constitutive Stat-3 dependent Src transformation with no effect on Stat-3 independent Ras transformation. The unphosphorylated inactive control peptide is also available under Cat. No.573105.	1mg 5 mg
STAT3 Inhibitor Peptide, Inactive Control	**573105**	**[NH_2-PYLKTKAAVLLPVLLAAP-CO_2H; PYLKTK-mts (mts - membrane translocating sequence)]** A cell-permeable, non-phosphorylated inactive control peptide for STAT3 cellular function studies utilizing STAT3 Inhibitor PpYLKTK-mts (Cat. No.573096).	5 mg
STAT3 Inhibitor V, Stattic	**573099**	**(Stat three inhibitory compound; 6-Nitrobenzo[b]thiophene-1,1-dioxide)** A cell-permeable vinyl-sulfone compound that acts as an inhibitor of STAT3 cellular function by targeting the STAT3-SH2 domain and preventing its association with upstream kinases. The effect of Stattic towards STAT family members is temperature-dependent and appears to be highly STAT3-selective at 37˚C. Shown to inhibit cellular phosphorylation of STAT3 at Tyr^{705} with little effect towards STAT1 phosphorylation at Tyr^{701} (in HepG2 cells) or the phosphorylation of JAK1, JAK2, and c-Src (in MDA-MB-231 and MDA-MB-235S cells).	25 mg
STAT3 Inhibitor VI	**573102**	**[S3I-201; NSC 74859; 2-Hydroxy-4-(((4-methylphenyl) sulfonyloxy)acetyl)amino)-benzoic acid]** A cell-permeable amidosalicylic acid compound that binds Stat3-SH2 domain and prevents Stat3 phosphorylation/activation, dimerization, DNA-binding, and Stat3-dependent transcription. Shown to arrest Stat3-dependent tumor growth both in cultures *in vitro* (effective conc. ≤100 µM) and in a murine xenograft model *in vivo* (5 mg/kg, i.v.).	10 mg
STAT3 Inhibitor VII	**573103**	**[Ethyl-1-(4-cyano-2,3,5,6-tetrafluorophenyl)-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate]** A cell-permeable dihydroquinoline compound that potently and specifically inhibits cellular JAK1/JAK2/TYK2/STAT3 activation (IC_{50} against U266 constitutive STAT3 Y750 phosphorylation =170 nM) as well as the transcription of STAT3 target genes, while exhibiting little effects against pathways involved in Akt/mTOR, Erk1/2, or STAT5 activation. Since the inhibitor does not affect JAK1/2/3 kinase activity, its cellular target(s) appears to be upstream of JAKs.	5 mg
STAT3 Inhibitor VIII, 5,15-DPP	**573109**	**5,15-Diphenylporphyrin** A cell-permeable porphyrin compound that binds STAT3 (K_D = 880 nM by SPR) and prevents STAT3 SH2 domain-mediated ligand binding (IC_{50} = 280 nM) and dimerization (~60% inhibition at 50 µM in HEK293), while exhibiting much reduced activity against STAT1 ligand binding (IC_{50} = 10 µM) and no activity againt Grb2 ligand binding even at concentrations as high as 20 µM. One day 5,15-DPP pre-treatment (50 µM) of MDA-MB-468 cultures is shown to greatly inhibit IL-6-induced STAT3, but not STAT1/5a/5b, nuclear translocation (by >90%) and nuclear STAT3 c-myc promoter binding activity, resulting in a more than 90% reduction in cellular c-myc protein level.	25 mg
STAT5 Inhibitor	**573108**	**[N'-((4-Oxo-4H-chromen-3-yl)methylene)nicotinohydrazide]** A cell-permeable nonpeptidic nicotinoyl hydrazone compound that selectively targets the SH2 domain of STAT5 (IC_{50} = 47 µM against STAT5b SH2 domain EPO peptide binding activity), while exhibiting much less effect towards the SH2 domain of STAT1, STAT3, or Lck (IC_{50} >500 µM). Shown to block STAT5/STAT5 DNA binding activity in K562 nuclear extract and inhibit IFN-α-stimulated STAT5, but not STAT1 or STAT3, tyrosine phosphorylation in Daudi cells.	10 mg

c-Jun N-Terminal Kinase (JNK/ SAP Kinase) Inhibitors

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, apoptosis, and participates in stress responses, such as those induced by hypoxin, cold shock, and hyperosmolarity. The three isoforms of JNK, known as JNK1, 2, and 3, are encoded by 3, independent genes. They phosphorylate Ser^{63} and Ser^{73} at the region of c-Jun and enhance its transcriptional activity. 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, endotoxins, and environmental stress. Its activation can mediate pro-inflammatory gene expression, cell proliferation and apoptosis.

MAP KINASE, MEK, AND JNK

c-Jun N-Terminal Kinase (JNK/SAP Kinase) Inhibitors

Product	Cat. No.	Comments	Size
Dicoumarol	**287897**	**[Bishydroxycoumarin; Dicumarol; 3,3'-Methylenebis(4-hydroxycoumarin)]** A cell-permeable quinone reductase inhibitor with anticoagulant properties. Potentiates apoptosis by simultaneously blocking SAPK/JNK and NF-κB pathways. Does not affect phosphorylation of p38 or activation of AKT. Blocks brefeldin A-dependent mono-ADP-ribosylation *in vitro* and Golgi disassembly in living cells (IC_{50} = 180 µM and 150 µM, respectively).	500 mg
JNK Inhibitor I, (L)-Form, Cell-Permeable	**420116**	**[(*L*)-HIV-TAT_{48-57}-PP-JBD_{20}; (L)-JNKI1; c-Jun NH_2-terminal kinase; H-GRKKRRQRRRPPPRPKRPTTLNLFPQVPRSQDT-NH_2; SAPK Inhibitor I]** 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. Blocks c-Jun NH_2-terminal kinase (JNK) signaling by preventing the activation of the transcription factor c-*jun* (IC_{50} ~ 1 µM). This effect appears to be due to inhibition of phosphorylation of the activation domains of JNK. Contains the minimal 20-amino acid inhibitory domain of islet-brain (IB) that is shown to be critical for interaction with JNK linked to the 10-amino acid HIV-TAT_{48-57} sequence as a carrier peptide and two proline residues as spacer. Inhibits IL-1ß-induced c-*jun* and c-*fos* expression in insulin secreting ßTC-3 cells and offers protection against apoptosis. Does not affect insulin secretion and has no effect on either ERK 1/2 or p38 activities.	1 mg
JNK Inhibitor I, (L)-Form, Cell-Permeable, Negative Control	**420118**	**[(L)-HIV-TAT_{48-57}-PP; GRKKRRQRRRPP-NH_2]** A highly cell-permeable 10-amino acid carrier peptide derived from HIV-TAT_{48-57} sequence that is modified with two proline residues. Shown to accumulate into a variety of cells. Serves as a useful negative control for studies involving JNK Inhibitor I, (L)-Form, Cell-Permeable (Cat. No.420116).	1 mg
JNK Inhibitor II	**420119**	**{Anthra[1,9-*cd*]pyrazol-6(2*H*)-one; 1,9-pyrazoloanthrone; SAPK Inhibitor II; SP600125}** A potent, cell-permeable, selective, and reversible inhibitor of c-Jun N-terminal kinase (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. Inhibits the phosphorylation of c-Jun and blocks cellular expression of IL-2, IFN-γ, TNF-α, and COX-2. Blocks IL-1-induced accumulation of phospho-Jun and induction of c-Jun transcription. A 50 mM (5 mg/454 µl) solution of JNK Inhibitor II (Cat. No.420128) in DMSO is also available.	5 mg
InSolution™JNK Inhibitor II	**420128**	A 50 mM (5 mg/454 µl) solution of JNK Inhibitor II (Cat. No. 420119) in DMSO.	5 mg
JNK Inhibitor II, Negative Control	**420123**	**(N^1-Methyl-1,9-pyrazoloanthrone)** 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 SP600125 (IC_{50} = 40 nM and 90 nM, respectively).	1 mg
JNK Inhibitor III, Cell-Permeable	**420130**	**(Ac-YGRKKRRQRRR-gaba-ILKQSMTLNLADPVGSLKPHLRAKN-NH_2; HIV-TAT_{47-57}-gaba-c-Junδ_{33-57}; SAPK Inhibitor III)** A cell-permeable 37-mer peptide constructed by fusing human c-Jun δ domain (amino acids 33-57) sequence with that of HIV-TAT protein transduction domain (amino acids 47-57) via a γ-aminobutyric acid (GABA) spacer. Shown to specifically disrupt c-Jun/JNK complex formation and the subsequent phosphorylation and activation of c-Jun by JNK both *in vitro* and in intact cells. Since its mode of inhibition is different than that of JNK Inhibitor II (SP600125; Cat. No.420119), these two inhibitors can complement each other in JNK signaling pathway studies.	1 mg

MAP KINASE, MEK, AND JNK

c-Jun N-Terminal Kinase (JNK/SAP Kinase) Inhibitors *continued*

Product	Cat. No.	Comments	Size
JNK Inhibitor III, Cell-Permeable, Negative Control	**420131**	**(Ac-YGRKKRRQRRR-gaba-DSNLIRGVLPTLMPKSLAQNKLKHA-NH_2; HIV-TAT_{47-57}-gaba-c-Junδ_{33-57}, scrambled)** A cell-permeable 37-mer peptide that contains a scrambled human c-Jun δ domain (amino acids 33-57) sequence linked to that of HIV-TAT protein transduction domain (amino acids 47-57) via a γ-aminobutyric acid (GABA) spacer. Does not disrupt c-Jun/JNK complex formation and thus serves as a negative control for JNK Inhibitor III, Cell-Permeable (Cat. No.420130).	1 mg
JNK Inhibitor IX	**420136**	**[N-(3-Cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)-1-naphthamide]** A thienylnaphthamide compound that acts as a potent and ATP binding site-targeting inhibitor of JNK2 and JNK3 (pIC_{50} = 6.5 and 6.7, respectively) with little or no activity against JNK1, p38α, and a panel of more than 30 other kinases (pIC_{50} 50 = 6.4 and 5.9, respectively) under the same assay conditions.	5 mg
JNK Inhibitor V	**420129**	A cell-permeable pyrimidinyl compound that displays anti-inflammatory properties. Acts as a potent, reversible, and ATP-competitive inhibitor of *c*-Jun N-terminal kinase (JNK, IC_{50} = 150, 220, and 70 nM for hJNK1, hJNK2, and hJNK3, respectively) with a 10- to 100-fold greater selectivity over a panel of 25 other commonly studied kinases (IC_{50} typically in the range of 1-10 µM or no effect at 10 µM). Its *in vivo* efficacy has been demonstrated in gerbils, mice, and rats via oral, i.v., or i.p. administration.	5 mg
JNK Inhibitor VI, TI-$JIP_{153-163}$	**420133**	**(Truncated Inhibitor based on JNK-Interacting Protein 1; H2N-RPKRPTTLNLF-NH_2)** A murine JIP-1 JNK-binding domain- (JBD) derived 11-mer peptide that directly interacts with JNK (K_D in low µM range) and specifically inhibits JNK kinase activity without inhibitory effects towards ERK or p38. The inhibition is not limited only to JBD-containing substrates and is found to be mixed/non-competitive with respect to ATP. JNK Inhibitor VII, TAT-TI-$JIP_{153-163}$, Cell-Permeable, is also available (Cat. No.420134).	2 mg
JNK Inhibitor VII, TAT-TI-$JIP_{153-163}$, Cell-Permeable	**420134**	**(TAT38-48 -Truncated Inhibitor based on JNK-Interacting Protein 1; H2N-YGRKKRRQRRR-RPKRPTTLNLF-NH_2)** The non-permeant JNK inhibitor peptide TI-$JIP_{153-163}$ (Cat. No.420133) is made cell-permeable with an N-terminal TAT protein transduction domain sequence. Shown to offer neuroprotection in a rat ischemic brain injury model in *in vivo*.	2 mg
JNK Inhibitor VIII	**420135**	**[N-(4-Amino-5-cyano-6-ethoxypyridin-2-yl)-2-(2,5-dimethoxyphenyl)acetamide]** A cell-permeable pyridinylamide compound that acts as an ATP-competitive, reversible inhibitor of JNK (K_i = 2 nM, 4 nM and 52 nM for JNK1, 2 and 3, respectively) and displays excellent selectivity over 72 other kinases. Inhibits c-jun phosphorylation with an EC_{50} of 920 nM in HepG2 cells. Preferentially blocks the growth of PTEN null mouse embryonic fibroblasts.	5 mg
JNK Inhibitor X, BI-78D3	**420140**	**4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-(5-nitrothiazol-2-ylthio)-4H-1,2,4-triazol-3-ol** A cell-permeable benzodioxin-triazole compound that competes with JNK-interacting protein-1 (IC_{50} = 500 nM in competitive binding to JNK1 with pepJIP1) and D-domain-containing substrates binding (K_i = 200 nM in competitive binding to JNK1 with ATF2) by targeting JNK JIP1-interacting site (K_d = 8.1 µM). BI-78D3 inhibits the phosphorylation of ATF2, but not that of a D-domain-less peptide substrate, by JNK1 in kinase assays, while showing 100-fold less potency against p38α and no effect against mTOR or PI3-Kα. Shown to inhibit the TNF-α-stimulated GFP-cJun phosphorylation in transfected HeLa cultures *in vitro* (IC_{50} = 12.4 µM) and effectively reduce ConA-induced murine liver failure (10 mg/kg, i.p.) as well as restore insulin sensitivity in a murine type 2 diabetes model (25 mg/kg, i.p.) *in vivo*.	5 mg
NPPB	**484100**	**5-Nitro-2-(3-phenylpropylamino)benzoic Acid** Potent Cl^- channel blocker (IC_{50} = 100 nM-100 µM), depending on channel subtype and assay method. Inhibits cyclooxygenase (IC_{50} = 8 µM).	10 mg
Protein Kinase Inhibitor, DMAP	**476493**	**(N^6,N^6-Dimethyladenine; 6-Dimethylaminopurine; 6 DMAP)** A puromycin analog that acts as a protein kinase inhibitor. Selectively induces premature mitosis in mammalian cells. Inhibits TNF-α upregulation of ICAM-1, lipolysis, and the activation of JNK/SAPK. Inhibits p34cdc2/cyclin B (IC_{50} = 300 µM). Induces apoptosis in S-phase-arrested HeLa cells (~5 mM).	50 mg

Mitogen-Activated Protein (MAP) Kinase Inhibitors

The mitogen-activated protein (MAP) kinases are a group of evolutionarily conserved 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 transcription factors in a pattern unique to a given external signal. Although MAP kinases are expressed in all cell types, they regulate very specific biological responses that differ from cell type to cell type.Four major types of MAP kinase cascades have been reported in mammalian cells that respond synergistically to different upstream signals. MAP kinases are part of a three-tiered phospho-relay cascade consisting of MAP kinase, a MAP kinase kinase (MEK) and a MAP kinase kinase kinase (MEKK). 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, at any given time one highly active form of ERK1 or ERK2 (dual phosphorylated) exists, which exhibits over 1000-fold greater activity than the unphosphorylated form. ERKs can translocate to the nucleus to phosphorylate Elk-1 (on Ser^{383} and Ser^{389}). 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 JNK/SAPK 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 upstream 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.

The fourth and least studied mammalian MAP kinase pathway is big MAP kinase 1 (BMK1), also known as extracellular signal regulated kinase 5 (ERK5). BMK1 is activated in response to growth factors and stress. Activation of the BMK1 signaling pathway has not only been implicated in normal cell survival, cell proliferation, cell differentiation, but also in pathological states such as carcinogenesis, cardiac hypertrophy, and atherosclerosis. BMK1 can be activated following exposure EGF, BDNF, NGF, VEGF, FGF-2, phorbol esters, and oxidative stress. The signaling molecules in the ERK5 cascade include MEKK2/3, MEK5, and ERK5. Since BMK1 is the only known substrate of MEK5, all effects of MEK5 have been attributed to its ability to activate BMK1. Thus far, myocyte enhancer factor 2 (MEF-2), Ets-domain transcription factor (Sap1a), Bad, and serum- and glucocorticoid-inducible kinase (SGK) have been identified as substrates for BMK1.

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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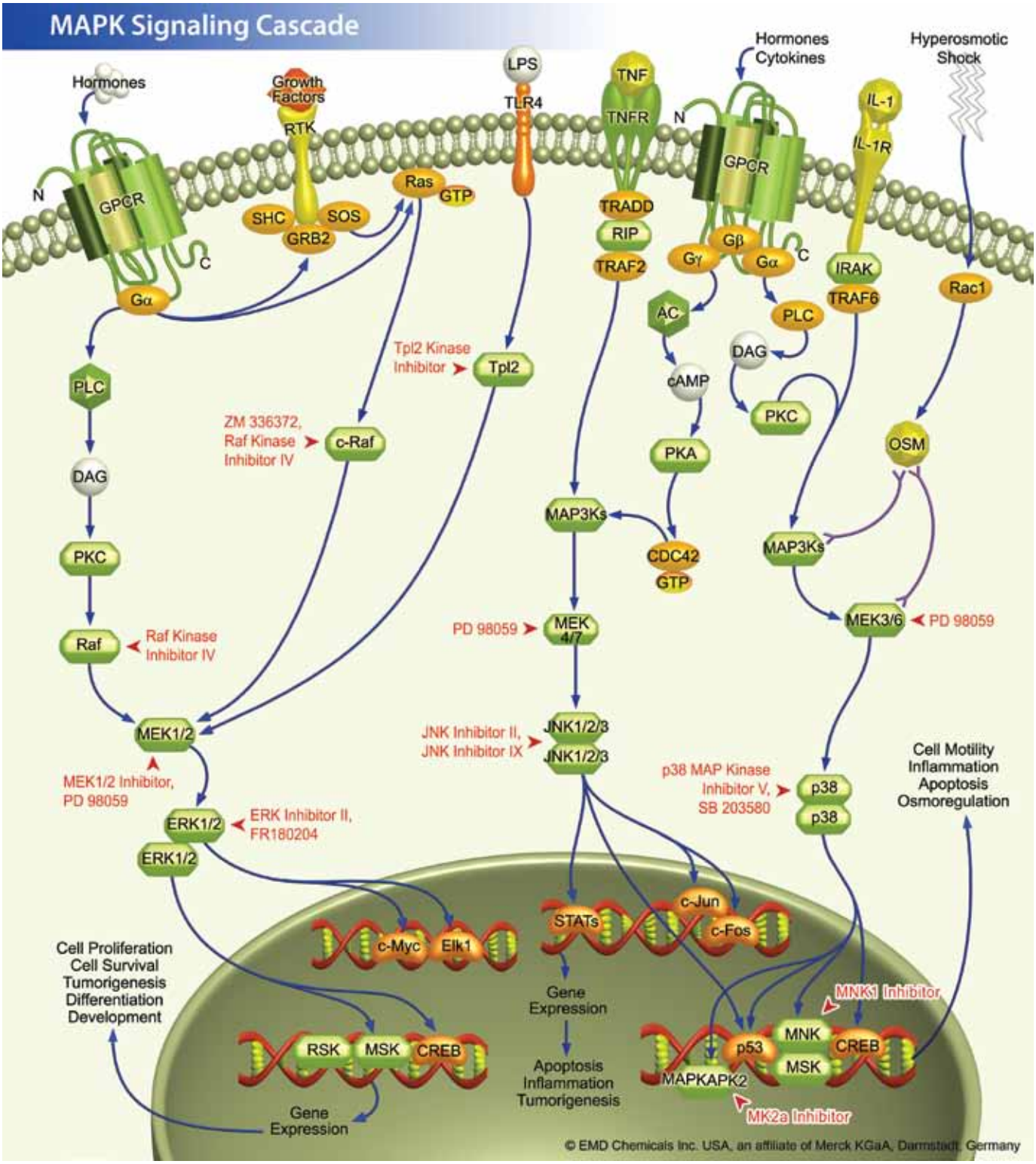
Highlighted below are inhibitors included in InhibitorSelect™ MAPK Signaling Pathway Inhibitor Panel (Cat. No. 444189). See page 31 or 204 for details.



MAP KINASE, MEK, AND JNK

MAP Kinase Inhibitors

Product	Cat. No.	Comments	Size
AG 126	**658452**	**[α-Cyano-(3-hydroxy-4-nitro)cinnamonitrile]** A cell-permeable inhibitor of lipopolysaccharide (LPS)-induced synthesis of tumor necrosis factor-α and nitric oxide in murine peritoneal macrophages. Blocks LPS-induced tyrosine phosphorylation of a $p42^{MAPK}$/ERK2 protein substrate. Reduces the expression of iNOS and COX-2 in lungs of rats treated with carrageenan. Blocks glucocorticoid-induced COX-2 activity in human amnion cells (IC_{50} = 15.38 µM).	5 mg
Anthrax Lethal Factor, Recombinant, *Bacillus anthracis*	**176900**	Recombinant, *Bacillus anthracis* anthrax lethal factor expressed in a specialized strain of *B. anthracis*. 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
Apigenin	**178278**	**4',5,7-Trihydroxyflavone** Induces the reversion of transformed phenotypes of v-H-*ras*-transformed NIH 3T3 cells at low concentration (12.5 µM). This finding has been attributed to the inhibition of MAP kinase activity. Inhibits the proliferation of malignant tumor cells by G_2/M arrest and induces morphological differentiation.	5 mg
ERK Activation Inhibitor Peptide I, Cell-Permeable	**328000**	**(Ste-$MEK1_{13}$; Ste-MPKKKPTPIQLNP-NH_2)** A cell-permeable and reversible stearated 13-amino acid peptide corresponding to the N-terminus of MEK1 (MAPKK) that acts as a specific inhibitor of ERK activation and blocks the transcriptional activity of Elk1. Selectively binds to ERK2 and prevents its interaction with MEK (IC_{50} = 2.5 µM). Potently blocks ERK activation in PMA-stimulated NIH 3T3 cells and NGF-treated PC12 cells (IC_{50} = 13 µM). Does not affect the activation of JNKs or p38.	1 mg
ERK Activation Inhibitor Peptide II, Cell-Permeable	**328005**	**(H-GYGRKKRRQRRR-G-MPKKKPTPIQLNP-NH_2; MTP_{TAT}-G-$MEK1_{13}$)** A cell-permeable and reversible 13-amino acid peptide corresponding to the N-terminus of MEK1 (MAPKK) 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 blocks the transcriptional activity of Elk1. Selectively binds to ERK2 and prevents its interaction with MEK (IC_{50} = 210 nM). Potently blocks ERK activation in PMA-stimulated NIH 3T3 cells and NGF-treated PC12 cells (IC_{50} = 29 µM). Does not affect the activation of JNKs or p38.	1 mg
ERK Inhibitor	**328006**	A cell-permeable and reversible thiazolidinedione compound that displays anti-proliferative properties ($IC_{50} \leq 25$ µM in HeLa, A549, and SUM-159 tumor cells). Preferentially binds to ERK2 with a K_D of ~5 µM and prevents its interaction with protein substrates. Shown to block ERK-mediated phosphorylation of ribosomal S6 kinase-1 (RSK-1) and ternary complex factor Elk-1 in HeLa cells, while exhibiting little effect on ERK1/2 phosphorylation by MEK1/2.	5 mg
ERK Inhibitor II, FR180204	**328007**	**5-(2-Phenyl-pyrazolo[1,5-a]pyridin-3-yl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine** A cell-permeable pyrazolopyridazin**amine** that acts as a potent, ATP-competitive inhibitor of ERK1 and ERK2 (IC_{50} = 510 nM and 330 nM; K_i = 310 nM and 140 nM, respectively). Exhibits ~20-fold greater selectivity over p38α (IC_{50} = 10 µM) and shows little activity towards IKKα, MEK1, MKK4, PDGFRα, PKCα, Src, and Syk even at concentrations as high as 30 µM. Shown to inhibit TGF-ß–induced AP-1 activation in Mv1Lu epithelial cells (IC_{50} = 3.1 µM). ERK Inhibitor II, Negative Control is also available (Cat. No.328008).	30 mg
ERK Inhibitor II, Negative Control	**328008**	**5-(2-Phenyl-pyrazolo[1,5-a]pyridin-3-yl)-1H-pyrazolo[3,4-c]pyridazin-3-ol** A cell-permeable pyrazolopyridazin**ol** that serves as a negative control for ERK Inhibitor II (Cat. No.328007). Shown to exhibit little activity towards ERK1 and ERK2 (IC_{50} > 100 µM) or in blocking TGF-ß–induced AP-1 activation in Mv1Lu epithelial cells (IC_{50} > 10 µM).	1 mg
ERK Inhibitor III	**328009**	A cell-permeable furanyl-nitroaminoguanidine ERK-binding (K_D = ~13 µM) compound that acts as a substrate-, but not ATP-, site-targeting inhibitor of ERK. Selectively inhibits the EGF-stimulated cellular phosphorylation of ERK substrates Rsk-1 and Elk-1, but not that of ERK1/2 or the anisomycin-induced phosphorylation of the p38 substrate ATP-2 in HeLa cells.	5 mg
Hsp25 Kinase Inhibitor	**385880**	**(KKKALNRQLGVAA; MAPKAP Kinase-2 Inhibitor; MK2 Inhibitor)** A 13-residue, cell-permeable peptide that acts as a potent and selective inhibitor of mammalian heat-shock protein (Hsp25) kinase [also called 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-competitive with respect to ATP (K_i = 134 µM).	1 mg

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MAP KINASE, MEK, AND JNK

MAP Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
InhibitorSelect™ MAP Kinase Signaling Pathway Inhibitor Panel	**444189**	A panel of 12 potent and selective inhibitors useful for the study of MAP kinase signaling pathway. This panel contains the following inhibitors: 1 mg of ERK Inhibitor II, FR180204 (Cat. No.328007); 5 mg of JNK Inhibitor II (Cat. No.420119); 5 mg of JNK Inhibitor IX (Cat. No.420136); 1 mg of MEK1/2 Inhibitor (Cat. No.444939); 5 mg of MNK1 Inhibitor (Cat. No.454861); 5 mg of MK2a Inhibitor (Cat. No.475863); 1 mg of p38 MAP Kinase Inhibitor V (Cat. No.506156); 5 mg of PD 98059 (Cat. No.513000); 1 mg of Raf Kinase Inhibitor IV (Cat. No.553014); 1 mg of SB 203580 (Cat. No.559389); 1 mg of Tpl2 Kinase Inhibitor (Cat. No.616373) and 1 mg of ZM 336372 (Cat. No.692000). Also provided with 15 ml of anhydrous DMSO.	1 ea
5-Iodotubercidin	**407900**	**{4-Amino-5-iodo-7-(ß-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine; ITU}** A cell-permeable, potent and competitive inhibitor of the MAP kinase ERK2 (K_i = 530 nM). Also inhibits adenosine kinase (K_i = 30 nM), serine/threonine kinases such as casein kinase I and PKA, and the insulin receptor kinase fragment (IC_{50} = 0.4-28 µM).	1 mg
p38 MAPKinase Inhibitor	**506126**	**[2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-1,2-dihydropyrazol-3-one]** A potent p38 MAP kinase inhibitor (IC_{50} = 35 nM).	500 µg
p38 MAPKinase Inhibitor III	**506121**	**{(RS)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}- (1-phenylethyl)amine]; ML3403}** A cell-permeable methylsulfanylimidazole compound that acts as a potent, selective, reversible, and ATP-competitive p38 MAP kinase inhibitor (IC_{50} = 0.38 µM for p38α). Shown to effectively suppresses LPS-induced cytokine release both *in vitro* (IC_{50} = 0.16 and 0.039 µM for TNF-α and IL-1ß release, respectively, in human PBMC) and *in vivo* (ED_{50} = 1.33 mg/kg for TNF-α release in mouse). When compared with SB 203580 (Cat. No.559389 and559398), it exhibits reduced inhibitory activity against cytochrome P450-2D6 isoform and, therefore, is better suited for *in vivo* use. A 10 mM (1 mg/247 µl) solution of p38 MAP Kinase Inhibitor III (Cat. No.506148) in DMSO is also available.	1 mg
MAP Kinase Cascade Inhibitor Set	**444185**	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).	1 set
MAP Kinase Inhibitor Set I	**444180**	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). Supplied with a data sheet.	1 set
MAP Kinase Inhibitor Set II	**444190**	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).	1 set
MK-2 Inhibitor III	**475864**	**{2-(2-Quinolin-3-ylpyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo-[3,2-c]pyridin-4-one}** A cell-permeable pyrrolopyridinyl compound that acts as an ATP-competitive inhibitor of MK-2/MAPKAP-K2 (IC_{50} = 8.5, 81, and 210 nM against MK-2, MK-5, and MK-3, respectively), while exhibiting much less or no activity against 8 other commonly studied kinases. Shown to suppress LPS-induced TNF-α production in U937 cells (IC_{50} = 4.4 µM).	5 mg
MK2a Inhibitor	**475863**	**[CMPD1; 4-(2'-Fluorobiphenyl-4-yl)-N-(4-hydroxyphenyl)-butyramide; Mitogen-activated protein kinase-activated protein kinase 2a Inhibitor]** A reversible *p*-amidophenolic compound that selectively inhibits the phosphorylation of MK2a (mitogen-activated protein kinase-activated protein kinase 2a; K_i^{app} = 330 nM) by p38α in a non-ATP-competitive manner. Does not block the kinase activity of p38α towards the other two known p38 substrates, MBP and ATF-2.	5 mg
InSolution™ML 3163	**475800**	**{4-[5-(4-Fluorophenyl)-2-(4-methanesulfinyl-benzylsulfanyl)-3H-imidazol-4-yl]pyridine}** A cell-permeable and reversible 2-benzylsulfanyl imidazole that combines the structural features of cytokine release inhibitors SKF-86002 (Cat. No.567305) and p38 MAP kinase inhibitor SB 203580 (Cat. No.559389). Acts as an effective inhibitor of TNF-α and IL-1ß release from mononuclear cells in human whole blood and peripheral blood mononuclear cells (IC_{50} = 20.3 µM and 3.65 µM for TNF-α; 2.78 µM and 0.88 µM for IL-1ß, respectively). Occupies the ATP binding site of p38 MAP kinase and inhibits its activity (IC_{50} = 4.0 µM).	1 mg
MNK1 Inhibitor	**454861**	**{4-Amino-5-(4-fluoroanilino)-pyrazolo[3,4-d]pyrimidine}** A cell-permeable, reversible, and ATP-competitive pyrazolo-pyrimidine compound that acts as a selective inhibitor of mitogen-activated protein kinase-interacting kinase 1 (MNK1; IC_{50} = 2.2 µM) with no inhibitory activity against p38, JNK1, ERK1/2, PKC, or Src-like kinases. Effectively inhibits eIF4E phosphorylation (IC_{50} = 3 µM) by MNK1 in 293 human embryonic kidney cells and serves as a useful tool in studying MNK1-mediated cellular signaling.	5 mg
NPPB	**484100**	**5-Nitro-2-(3-phenylpropylamino)benzoic Acid** Potent Cl^- channel blocker (IC_{50} = 100 nM-100 µM), depending on channel subtype and assay method. Inhibits cyclooxygenase (IC_{50} = 8 µM).	10 mg

MAP KINASE, MEK, AND JNK

MAP Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
InSolution™p38 MAP Kinase Inhibitor III	**506148**	A 10 mM (1 mg/247 µl) solution of p38 MAP Kinase Inhibitor III (Cat. No. 506121) in DMSO.	1 mg
p38 MAP Kinase Inhibitor IV	**506153**	**[MT4; 2,2'-Sulfonyl-bis-(3,4,6-trichlorophenol)]** A cell-permeable symmetrical sulfone compound that acts as a potent and ATP-competitive inhibitor of p38α/ß MAPK (IC_{50} = 130 and 550 nM, respectively), while exihibiting much reduced activity (≤23% inhibition at 1 µM) against p38γ/δ, ERK1/2, and JNK1/2/3. Shown to be more effective than SB 203850 (Cat. Nos.559389,559395, and559398) in inhibiting LPS-induced IL-1ß release from hPBMC (100% vs. 50% inhibition with 100 µM respective inhibitor).	10 mg
p38 MAP Kinase Inhibitor IX	**506161**	**{N-(Isoazol-3-yl)-4-methyl-3-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)benzamide}** A cell-permeable pyrazolo-pyrimidine compound that acts as a potent ATP-binding pocket-targeting inhibitor against p38α MAP kinase activity (IC_{50} = 5 nM; K_i = 0.2 nM), while exhibiting little or no activity against a panel of 21 other commonly studied kinases and 5 CYP 450 isozymes (IC_{50} ≥40 µM). Shown to be orally active in mice with excellent pharmacokinetics and *in vivo* efficacy in lowering (>70%; 5 mg/kg p.o. 5 h prior to LPS challenge) LPS-induced plasma TNFα production.	2 mg
p38 MAP Kinase Inhibitor V	**506156**	**[SC-409; 4-(3-(4-Chlorophenyl)-5-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)pyrimidine]** A cell-permeable trisubstituted pyrazole compound that acts as a highly potent ATP-competitive inhibitor of CK1δ and p38α (IC_{50} = 20 and 40 nM, respectively). Shown to affect p38ß, PKA, JNK2, and JNK3 activity (IC_{50} = 2.3, 10.5, 19.7, and 69.7 µM, respectively) only at much higher concentations and exhibit little effect against a panel of 44 other commonly studied kinases, including p38δ/γ, even at a conentraion of 10 µM or higher. An excellent tool for studying p38-mediated responses both in cells *in vitro* and in animals *in vivo*.	1 mg
p38 MAP Kinase Inhibitor VI	**506157**	**[JX401; N-(2-Methoxy-4-thiomethyl)benzoyl-4-benzylpiperidine]** A cell-permeable piperidinamide compound that acts as a reversible and highly potent inhibitor of MAPK p38α (IC_{50} = 32 nM) with no detectable activity against p38γ even at concentrations as high as 10 µM. Shown to effectively block the differentiation of L8 myoblasts to myotubes at 10 µM in a reversible manner. Not a competitive inhibitor with respect to either ATP or substrate.	5 mg
p38 MAP Kinase Inhibitor VII	**506158**	**(SD-169; Indole-5-carboxamide)** A cell-permeable indole compound that acts as a potent, ATP-competitive, and isozyme-selective p38α MAP kinase inhibitor (IC_{50} = 3.2 nM). It inhibits p38ß only at much higher concentrations (IC_{50} = 122 nM) and exhibits little activity against p38γ, ERK2, JNK-1, or MAPKAPK-2 even at concentrations as high as 50 µM. When administered to NOD mice via food intake *in vivo*, SD-169 is shown to prevent the development of type 1 diabetes in prediabetic mice and display therapeutic efficacy in treating animals already in mild and moderate hyperglycemic states.	10 mg
p38 MAP Kinase Inhibitor VIII	**506163**	**[(4-((2-Amino-4-bromophenyl)amino)-2-chlorophenyl)-(2-methylphenyl)methanone]** A cell-permeable aminobenzophenone compound that acts as a potent, ATP-binding pocket-targeting inhibitor against p38α and p38$ß_2$ (82% and 93% inhibition with 1 µM inhibitor, respectively; IC_{50} of p38α inhibition = 40 nM) with little activity against a panel of 57 other kinases, including p38γ, p38δ, Erk1/2, and JNK1. Shown to inhibit LPS-induced cytokine productions in human PBMC's *in vitro* and exhibit *in vivo* efficacy in both acute and chronic murine models of skin inflammation.	5 mg
PD 169316	**513030**	**[4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole]** A potent, cell-permeable, reversible, competitive, and selective p38 MAP kinase inhibitor (IC_{50} = 89 nM). Inhibition of p38 MAP kinase by PD 169316 blocks apoptosis induced by trophic factor withdrawal in non-neuronal and neuronal cell lines.	1 mg
PD 98059	**513000**	**(2'-Amino-3'-methoxyflavone)** Selective, reversible, and cell-permeable inhibitor of MAP kinase kinase (MEK) that acts by inhibiting the activation of MAP kinase and subsequent phosphorylation of MAP kinase substrates. Pretreatment of PC-12 cells with PD 98059 completely blocks the 4-fold increase in MAP kinase activity produced by nerve growth factor (NGF; IC_{50} = 2 µM); however, it has no effect on NGF-dependent tyrosine phosphorylation of the $p140^{trk}$ receptor or its substrate Shc and does not block NGF-dependent activation of PI 3-kinase. Blocks LPS-induced activation of TNF-α gene expression. Inhibits cell growth and reverses the phenotype of *ras*-transformed BALB3T3 mouse fibroblasts and rat kidney cells. A 5 mg/ml solution of PD 98059 (Cat. No.513001) in anhydrous DMSO is also available.	5 mg

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MAP KINASE, MEK, AND JNK

MAP Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
SB 202190	**559388**	**[FHPI; 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole]** A potent, reversible, competitive, and cell-permeable inhibitor of p38 MAP kinase. Inhibits p38 phosphorylation of myelin basic protein (MBP) with no effect on the activity of the ERK or JNK MAP kinase subgroups. Also inhibits the kinase activity of p38ß (K_i = 16 nM; IC_{50} = 350 nM) and p38 phosphorylation of activating transcription factor 2 (ATF-2; IC_{50} = 280 nM). Blocks LPS-induced TNF-α and interleukin biosynthesis. Reported to induce LDL receptor expression in Hep52 cells. A 1 mg/ml solution of SB 202190 (Cat. No.559397) in anhydrous DMSO is also available.	1 mg
InSolution™SB 202190	**559397**	A 1 mg/ml solution of SB 202190 (Cat. No. 559388) in anhydrous DMSO.	1 ml
SB 202190, Hydrochloride	**559393**	**4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole, HCl** A water-soluble form of the potent p38 MAP kinase inhibitor SB 202190 (Cat. No.559388).	1 mg
SB 202474	**559387**	**[4-Ethyl-2(p-methoxyphenyl)-5-(4'-pyridyl)-IH-imidazole]** A negative control for SB202190 (Cat. No. 559388) and SB203580 (Cat. No. 559389) in p38 MAP kinase inhibition studies.	1 mg
SB 202474, Dihydrochloride	**559407**	**[4-Ethyl-2(p-methoxyphenyl)-5-(4'-pyridyl)-IH-imidazole, DiHCl]** A water-soluble form of SB 202474 (Cat. No.559387). Useful as a negative control for SB202190, HCl (Cat. No.559393) and SB203580, HCl (Cat. No.559395) in p38 MAP kinase inhibition studies.	1 mg
SB 203580	**559389**	**[4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole]** A highly specific, potent, cell-permeable, selective, reversible, and ATP-competitive inhibitor of p38 MAP kinase (IC_{50} = 34 nM *in vitro*, 600 nM in cells). Does not significantly inhibit the JNK and p42 MAP kinase at 100 µM. Inhibits IL-1 and TNF-α production from LPS-stimulated human monocytes and the human monocyte cell line THP-1 (IC_{50} = 50-100 nM). Inhibits bone morphogenetic protein-2-induced neurite outgrowth in PC12 cells. Also inhibits platelet aggregation caused by collagen (IC_{50} = 0.2-1.0 µM) or the thromboxane analog U-46619 (Cat. No.538944). A 1 mg/ml solution of SB 203580 (Cat. No.559398) in anhydrous DMSO is also available.	1 mg
InSolution™SB 203580	**559398**	A 1 mg/ml solution of SB 203580 (Cat. No. 559389) in anhydrous DMSO.	1 ml
SB 203580, Hydrochloride	**559395**	**4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole, HCl** A water-soluble form of the potent MAP kinase inhibitor SB 203580 (Cat. No.559389).	1 mg
SB 203580, Iodo-	**559400**	**[4-(3-Iodophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole]** A highly specific, cell-permeable, reversible, ATP-competitive, and potent inhibitor of p38 MAP kinase. Exhibits similar inhibitory potency as its parent compound SB 203580 (Cat. No.559389). Useful for the identification of inhibitor binding sites in p38 MAP kinase.	1 mg
SB 203580, Sulfone	**559399**	**[4-(4-Fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole]** A cell permeable, reversible, and ATP-competitive sulfone analog of the p38 MAP kinase inhibitor SB 203580 (Cat. No.559389). Potently inhibits p38 kinase (IC_{50} = 30 nM) and inhibits IL-1 production in human monocytes (IC_{50} = 200 nM).	1 mg
SB 220025	**559396**	**[5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinlyl)imidazole]** A cell-permeable, potent, reversible, ATP-competitive, and specific inhibitor of human p38 MAP Kinase (IC_{50} = 60 nM). Binds to an extended pocket in the active site of the enzyme. Exhibits over 2000-fold greater selectivity for p38 MAPK over ERK (p42/p44 MAP kinase), 500-fold over PKA, 50-fold over PKC, and >1000-fold over EGFR. Also acts as a potent inhibitor of angiogenesis and as an inhibitor of LPS-induced TNF-α production.	500 µg
SB 239063	**559404**	**[*trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazole]** A potent, cell-permeable, reversible, and ATP-competitive inhibitor of the α- and ß-isoforms (IC_{50} = 44 nM), but not the γ- or δ-isoform (IC_{50} > 100 µM), of MAP kinase p38. It inhibits IL-1 and TNF-α production (IC_{50} = 120 nM and 350 nM, respectively) in LPS-stimulated human peripheral blood monocytes. Also reduces brain injury and neurological deficits in cerebral focal ischemia and reduces myocardial reperfusion injury by reducing the expression of endothelial adhesion molecule and by blocking polymorphonuclear (PMN) leukocytes accumulation.	500 µg
SC-68376	**565625**	**[2-Methyl-4-phenyl-5-(4-pyridyl)oxazole]** A potent, reversible, cell-permeable, ATP-competitive, and selective inhibitor of p38 MAP kinase activity in a dose-dependent manner (IC_{50} = 2-5 µM). Does not inhibit basal ERK or IL-1-induced JNK activity.	1 mg

MAP KINASE, MEK, AND JNK

MAP Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
SKF-86002	**567305**	**{6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridyl)imidazo[2,1-b]thiazole}** A cell-permeable, reversible, and ATP-competitive cytokine-suppressive anti-inflammatory drug (CSAID). A bicyclic imidazole that inhibits lipolysaccharide (LPS)-stimulated human monocyte IL-1 and TNF-α production (IC_{50} = 1 µM). Also acts as an inhibitor of both cyclooxygenase and 5-lipoxygenase. SKF-86002 also acts as a specific p38 MAP kinase inhibitor.	5 mg
Tpl2 Kinase Inhibitor	**616373**	**{4-(3-Chloro-4-fluorophenylamino)-6-(pyridin-3-yl-methylamino)-3-cyano-[1,7]-naphthyridine}** A cell-permeable naphthyridine compound that acts as a potent, reversible, and ATP-competitive inhibitor of Tpl2 kinase (IC_{50} = 50 nM). Displays significant selectivity over other related kinases (IC_{50} = 5, >40, 110, 180, >400 and >400 µM for EGFR, MEK, MK2, p38, Src, and PKC, respectively). Shown to inhibit LPS-induced TNF-α production both from primary human monocytes and in whole blood (IC_{50} = 700 nM and 8.5 µM, respectively).	1 mg
Tpl2 Kinase Inhibitor II	**616404**	**4-(Cycloheptylamino)-6-(pyridin-3-yl-methylamino)-3-cyano-[1,7]-naphthyridine, hydrate, Tumor Progression Locus 2 Kinase Inhibitor II** A cell-permeable naphthyridine-cyclohexyl Tpl2 Kinase Inhibitor (Cat. No.616373) analog that acts as a potent ATP-competitive Tpl2 inhibitor (IC_{50} = 160 nM) with little activity (IC_{50} >20 µM) against EGFR, Src, MEK, p38, PKA, PKC, or S6. Reported to block LPS-induced TNF-α production both *in vitro* (IC_{50} = 0.5 and 4.5 µM using human monocytes and whole blood, respectively) and in rats *in vivo* (10 mg/kg, i.p.).	1 mg
U0124	**662006**	**[1,4-Diamino-2,3-dicyano-1,4-*bis*(methylthio)butadiene]** A useful negative control for MEK inhibitors U0125 (Cat. No.662008) and U0126 (Cat. No.662005). Does not inhibit MEK activity even at concentrations of 100 µM.	1 mg
U0125	**662008**	**[1,4-Diamino-2,3-dicyano-1,4-*bis*(phenylthio)butadiene]** A specific inhibitor of MEK (MEK1 and MEK2). Structurally similar to U0126 (Cat. No.662005) but about 10-fold less potent. Noncompetitive with respect to ATP.	1 mg
U0126	**662005**	**[1,4-Diamino-2,3-dicyano-1,4-*bis*(2-aminophenylthio)butadiene]** A potent and specific inhibitor of MEK1 (IC_{50} = 72 nM) and MEK2 (IC_{50} = 58 nM). The inhibition is noncompetitive with respect to both ATP and ERK. Has very little effect on other kinases such as Abl, Cdk2, Cdk4, ERK, JNK, MEKK, MKK-3, MKK-4/SEK, MKK-6, PKC, and Raf. Also acts as an immunosuppressant by effectively blocking IL-2 synthesis and T cell proliferation without affecting the long-term outcomes of either T cell activation or tolerance. Noncompetitive with respect to ATP.	1 mg
UCN-01	**539644**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp; 7-Hydroxystaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derived anticancer agent that reversibly and ATP-competitively inhibits several protein kinases (IC_{50} = 29 nM, 34 nM, 30 nM, 590 nM and 530 nM for PKCα, PKCß, PKCγ, PKCδ and PKC; IC_{50} = 7 nM, 27 nM, 50 nM, 50 nM, 150 nM and 1.04 µM for Chk1, Cdc25C-associated protein kinase 1, Cdk1, PAK4, Cdk5/p25 and Chk2; IC_{50} = 33 nM, 50 nM, 95 nM, 500 nM, 500 nM and 1.0 µM for PDK1, lck, MAPKAP kinase-2, Akt, GSK-3ß and PKA, respectively). At higher concentrations (> 15 µM), affects the activities of Src, PIM-1, CKII, DNA-PK, ErK1, ILK-1 and MAPKK1). Reported to suppress thymidylate synthase expression, induce apoptosis with caspase activation, and sensitize tumor cells to a range of DNA-damaging agents.	500 µg
ZM 336372	**692000**	**{N-[5-(3-Dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide}** A potent, cell-permeable, reversible, ATP-competitive and specific inhibitor of the protein kinase c-Raf (IC_{50} = 70 nM). Inhibits c-Raf with ten-fold increased potency compared to B-Raf, but does not inhibit many other protein kinases (even at 50 µM) with the exception of SAPK2a/p38α (IC_{50} = 2 µM) and SAPK2b/p38ß2 (IC_{50} = 2 µM). The inhibition of c-Raf by ZM 336372 is competitive with respect to ATP.	1 mg

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MAP KINASE, MEK, AND JNK

MEK Inhibitors

Product	Cat. No.	Comments	Size
MEK Inhibitor I	**444937**	A cell-permeable pyridine-containing vinylogous cyanamide compound that acts as a potent and selective inhibitor of MEK (IC_{50} = 12 nM) with little activity towards MKK3 and MKK4 (IC_{50} > 1 µM). The inhibition is noncompetitive with respect to ERK and the compound displays significant affinity only towards ATP-bound MEK (i.e. noncompetitive with respect to ATP). Exhibits superior potency, solubility, and stability compared to U0126 (Cat. No.662005) in aqueous solutions. Shown to protect against phorbol ester-mediated ear edema in mice (ED_{50} of 5 mg/kg, ip.).	1 mg 5 mg
MEK Inhibitor II	**444938**	**[2-Chloro-3-(N-succinimidyl)-1,4-naphthoquinone]** A cell-permeable 1,4-naphthoquinone compound that acts as potent and selective inhibitor of MEK (IC_{50} = 0.38 µM for MEK1). It shows little effect on PKC and PKA, and inhibits Raf1 and ERK1 only at much higher concentrations (IC_{50} = 34.5 and 82.9 µM, respectively).	5 mg
MEK Inhibitor Set	**453710**	Contains 5 mg of PD 98059 (Cat. No.513000), 1 mg of U0126 (Cat. No.662005), and 1 mg of the negative control U0124 (Cat. No.662006). Supplied with a data sheet.	1 set
MEK1/2 Inhibitor	**444939**	**[Z-& E-α-(Amino-((4-aminophenyl)thio)methylene)-2-(trifluoromethyl) benzeneacetonitrile; SL327]** A cell-permeable vinylogous cyanamide that acts as a selective inhibitor of MEK1/2 (IC_{50} = 180 nM and 220 nM, respectively). Shown to inhibit AP-1 activity (IC_{50} = 2.03 µM). Inhibits ERK1, MKK3/p38, MKK4, JNK, and PKC activities at higher concentrations (IC_{50} > 10 µM). Reported to offer neuroprotection against ischemic brain injury in mice by selectively blocking ERK1/2 activation. Also suppresses IL-1ß expression. Displays enhanced aqueous solubility compared to U0126 (Cat. No.662005). Uncompetitive with respect to ATP.	1 mg 5 mg
MEK1/2 Inhibitor II	**444965**	**[N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methylphenylamino)benzamide]** A cell-permeable and orally available amino-benzamide compound that acts as a potent and non-ATP-competitive inhibitor of MEK1/2 (IC_{50} = 8 nM) with an excellent selectivity over ERK, c-Src, Cdk's, and PI 3-Kγ (IC_{50} >1.0 µM). Reported to exhibit *in vivo* efficacy in several animal models of arthritis and hyperalgesia in rat and rabbit.	5 mg
MEK1/2 Inhibitor III	**444966**	**N-((2R)-2,3-Dihyroxypropoxy)-3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-benzamide, PD0325901, PD325901** A cell-permeable benzamide compound that acts as a non-competitive, highly potent, selective MEK/MAPKK/MKK inhibitor and effectively blocks cellular Erk1/2 phosphorylation (by >90% in serum-starved HeLa after serum-stimulation and 50% in C26 with 25 and 0.33 nM inhibitor, respectively), while exhibiting little or no effect against the activity of Erk1/2 or a panel of 66 other kinases even at concentrations as high as 10 µM in cell-free kinase assays. Shown to be orally available in mice and suppress both the growth of and Erk phosphorylation in BRAF(V600E)-expressing SKMEL28 cell-derived tumor *in vivo*.	5 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 (DSPs), 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 phosphotyrosine or phosphothreonine, enabling transition-state stabilization, and the aspartate enhances catalysis by protonating oxygen on the departing phosphate group. All DSPs contain two conserved regions, known as the CH2 domains, at their amino terminus, which are involved in substrate binding. In addition, they contain a MAP kinase-docking site at the amino terminus that consists of a cluster of positively charged amino acids. The corresponding docking site on MAP kinases consists of negatively charged residues indicating that electrostatic interactions are involved in binding of MAP kinases and MKPs. The group III DSPs also have an extended carboxy terminus containing PEST sequences (abundant in proline, glutamate, serine and threonine) that are commonly found in rapidly degrading proteins. Removal of PEST sequences results in their stabilization.

DSP1, DSP2, DSP4, and DSP5 are located exclusively in the nucleus, whereas DSP6, DSP7, and DSP16 are predominantly expressed in the cytoplasm. DSP8, DSP9, and DSP10 exhibit both cytoplasmic and nuclear expression. Newly reported DSP18 and DSP21 are localized in the mitochondria.

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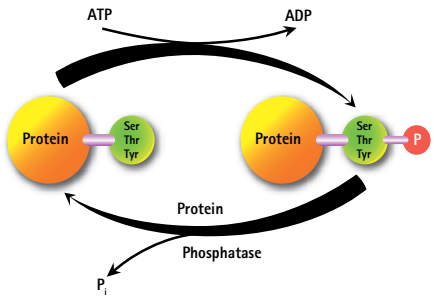

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Protein Phosphatase Inhibitors

Product	Cat. No.	Comments	Size
bpV(bipy)	**203694**	**[Potassium Bisperoxo(bipyridine)oxovanadate (V)]** A potent inhibitor of phosphotyrosine phosphatase (K_i = 100 nM for insulin receptor dephosphorylation). An activator of insulin receptor kinase (IRK). Also reported to be a potent inhibitor of PTEN (IC_{50} = 18 nM).	5 mg
bpV(HOpic)	**203701**	**[Dipotassium Bisperoxo(5-hydroxypyridine-2-carboxyl)oxovanadate (V)]** A potent phosphotyrosine phosphatase inhibitor. Activates the insulin receptor kinase (IRK) of hepatoma cells. Also stimulates lipogenesis in isolated adipocytes. Also reported to potently inhibit PTEN (IC_{50} = 14 nM).	5 mg
bpV(phen)	**203695**	**[Potassium Bisperoxo(1,10-phenanthroline)oxovanadate (V)]** A potent protein phosphotyrosine phosphatase inhibitor and insulin receptor kinase (IRK) activator. Excellent insulin mimetic at 15 µg/kg *in vitro* and *in vivo* for use. Inhibits the *in situ* dephosphorylation of autophosphorylated insulin receptors with over 1000-fold greater potency than sodium orthovanadate. Arrests proliferation of neuroblastoma NB 41 and glioma C6 cells at the G_2/M transition of the cell cycle. Also reported to potently inhibit PTEN (IC_{50} = 38 nM).	10 mg
bpV(pic)	**203705**	**[Dipotassium Bisperoxo(picolinato)oxovanadate (V)]** A potent phosphotyrosine phosphatase inhibitor. Activates the insulin receptor kinase (IRK) in hepatoma cells. A potent competitive inhibitor of glucose-6-phosphatase (K_i = 420 nM in intact microsomes). Also reported to potently inhibit PTEN (IC_{50} = 31 nM).	5 mg
Calcineurin Autoinhibitory Peptide	**207000**	**(ITSFEEAKGLDRINERMPPRRDAMP)** Specific calcineurin inhibitor. Corresponds to the C-terminal domain (residues 457-482) of the calmodulin-binding domain of calcineurin (PP2B). Inhibits Mn^{2+}-stimulated calcineurin activity (IC_{50} = 10 µM using ^{32}P-myosin light chain as a substrate) but has no effect on Ni^{2+}-stimulated enzyme activity. Does not inhibit CaM kinase II, protein phosphatase 1 or 2A.	250 µg
Calcineurin Autoinhibitory Peptide, Cell-permeable	**207001**	**(11R-CaN-AID; Ac-RRRRRRRRRRRGGGRMAPPRRDAMPSDA-NH_2)** A cell-permeable peptide that is composed of the calcineurin (CaN) autoinhibitory domain (AID) fused to a poly-arginine-based protein transduction domain (11R) and acts as an inhibitor of CaN phosphatase activity. Blocks CaN-dependent NFAT nuclear translocation and NFAT promoter activity in neurons. Protects neuronal cells from glutamate-induced cell death.	1 mg
Calyculin A, *Discodermia calyx*	**208851**	A cell-permeable inhibitor of protein phosphatase 2A (PP2A; IC_{50} = 0.5-1 nM) and protein phosphatase 1 (PP1; IC_{50} = 2 nM). A non-phorbol ester type tumor promoter that induces oxidative DNA damage. Selectively increases the efficacy of AMPA receptor-mediated synaptic transmission at excitatory synapses. Also known to prevent γ-radiation induced apoptosis in Burkitt's lymphoma cell line BM13674.	10 µg
CaMKP Inhibitor	**208775**	**(1-Amino-8-naphthol-2,4-disulfonic acid, Na salt, dehydrate; Ca^{2+}/Calmodulin-dependent Protein Kinase Phosphatase Inhibitor)** An amino-naphthol sulfonic acid that acts as a substrate-competitive inhibitor of Ca^{2+}/calmodulin-dependent protein kinase phosphatase (CaMKP) and its nuclear isoform CaMKP-N (IC_{50} = 6.4 and 6.6 µM, respectively), while exhibiting little activity against PP2B/CaN and PP2C (<10% inhibition at 10 µM).	100 mg
Cantharidic Acid	**210150**	**(5'-3'2,3-Dicarboxy-2,3-dimethyl-1,4-epoxycyclohexane; *exo*-1,6-Dicarboxy-*endo*-1, 6-dimethyl-7-oxabicylco[2,2,1]heptane)** A potent inhibitor of protein phosphatase 2A (IC_{50} = 50 nM).	10 mg
CDC25 Phosphatase Inhibitor, BN82002	**217691**	**[N-(2-Hydroxy-3-methoxy-5-dimethylamino)benzyl, N'-(2-(4-nitrophenethyl)), N"-methylamine]** A cell-permeable *ortho*-hydroxybenzylamino compound that displays antitumor properties. Acts as a potent, selective and irreversible inhibitor of CDC25 phosphatase family (IC_{50} = 2.4, 3.9, 6.3, 5.4, and 4.6 µM for 25A, 25B2, 25B3, 25C, and 25C-cat, respectively). Displays ~20-fold greater selectivity for CDC25 phosphatases over CD45 tyrosine phosphatase. Shown to delay cell cycle progression *in vitro* (IC_{50} = ~7.2-32.6 µM), and reduces tumor growth in athymic mice xenografted with the human pancreatic cells MIA PaCa-2 (15 mg/kg, i.p. route).	5 mg

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Protein Phosphatase Inhibitors *continued*

Product	Cat. No.	Comments	Size
CDC25 Phosphatase Inhibitor, NSC 663284	**217692**	**[6-Chloro-7-(2-morpholin-4-yl-ethylamino)quinoline-5,8-dione; DA3003-1]** A cell-permeable 7-substituted quinolinedione compound that displays antiproliferative properties. Acts as a potent, irreversible and mixed competitive inhibitor of the CDC25 phosphatase family (K_i = 29 nM, 95 nM and 89 nM for CDC25A, CDC25B2 and CDC25C, respectively; IC_{50} = 210 nM for CDC25B2) and displays nearly 20- and 450-fold greater selectivity for the CDC252 phosphatases over VHR and PTP1B (IC_{50} = 4.0 µM and > 100 µM, respectively). Reported to arrest cell cycle progression, inhibit Cdk dephosphorylation and delay tumor growth (IC_{50} = ~1.5 µM in NCI-60 tumor cell panel). Shown to modify CDC25A catalytic domain and to block cellular ERK dephosphorylation in HeLa-CDC25A cells.	5 mg
Cyclosporin A, *Tolypocladium inflatum*	**239835**	Cyclic oligopeptide with immunosuppressant properties. Induces apoptosis in rat thymocytes and in the murine B cell lymphoma cell line, WEH1-231. However, prevents anti-IgM and ionomycin-induced apoptosis in BLB cell lines. The complex of cyclosporin A with cyclophilin inhibits protein phosphatase 2B with nanomolar affinity. Inhibits nitric oxide synthesis induced by interleukin-1α, lipopolysaccharides, and TNF-α. Induces cardiomyocytes from embryonic stem cells.	100 mg
Cypermethrin	**239900**	**[(R,S)-α-Cyano-3-phenoxybenzyl-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate]** Synthetic type II pyrethroid. Potent inhibitor of calcineurin (protein phosphatase 2B; IC_{50} = 40 pM). May also have varied effects on ion channels.	10 mg
Deltamethrin	**253300**	**[(S)-α-Cyano-3-phenoxybenzyl(1R)-*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate]** Synthetic type II pyrethroid. Potent inhibitor of calcineurin (protein phosphatase 2B; IC_{50} = 100 pM). May also have varied effects on ion channels. Causes an increase in neurotransmitter release at synapses, and increases intrasynaptosomal Ca^{2+} levels.	10 mg
Dephostatin	**263200**	Protein tyrosine phosphatase inhibitor. Competitively inhibits protein tyrosine phosphatase activity in membrane preparations from human neoplastic T cell line (IC_{50} = 7.7 µM). Reported to mobilize intracellular calcium stores. Could serve as a stable NO donor for S-nitrosylation of proteins.	1 mg
3,4-Dephostatin	**263202**	**(3,4-Dihydroxy-N-methyl-N-nitrosoaniline)** A protein tyrosine phosphatase inhibitor (IC_{50} = 18 µM) that enhances growth factor-induced differentiation in PC12 cells possibly by sustaining MAP kinase activity. Can also be used as a protein S-nitrosylating agent. Exhibits greater stability than Dephostatin (Cat. No.263200).	1 mg
1,4-Dimethylendothall	**311250**	**(1,4-Dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid)** A useful negative control for the protein phosphatase inhibitors Cantharidic Acid (Cat. No.210150), Cantharidin (Cat. No.210155), and Endothall (Cat. No.324760).	10 mg
eIF-2α Inhibitor, Salubrinal	**324895**	**(Sal)** A cell-permeable and selective inhibitor of the phosphatase complexes that dephosphorylate eukaryotic translation initiation factor 2 subunit α (eIF-2α). Shown to offer protection against ER stress-induced apoptosis (EC_{50} = ~15 µM in PC12 cells stimulated with 750 ng/ml of Tunicamycin (Cat. No.654380). Prevents HSV replication both in Vero cells (IC_{50} = ~3 µM for reducing plaque formation) *in vitro* and in a mouse cornea infection model *in vivo*.	5 mg
Endothall	**324760**	**(7-Oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid)** A cell-permeable, specific inhibitor of protein phosphatase 2A (PP2A, IC_{50} = 90 nM). Exhibits only a weak effect on PP1 (IC_{50} = 5 µM). Causes dose- and time-dependent cytostasis at the G_2/M phase in hepatocellular carcinoma cell lines.	20 mg
FBPase-1 Inhibitor	**344267**	**[F16BPase Inhibitor; 5-Chloro-2-(N-(2,5-dichlorobenzenesulfonamido))-benzoxazole]** A cell-permeable benzoxazolo-sulfonamide compound that inhibits hFBPase-1 (human fructose-1,6-bisphosphatase) enzymatic activity (IC_{50} = 3.4 µM) by competing at the AMP allosteric binding site. Shown to block glucose production in starved rat hepatoma cells (IC_{50} = 6.6 µM).	10 mg
Fenvalerate	**341380**	**[α-Cyano-3-phenoxybenzyl-α-(4-chlorophenyl)isovalerate]** A synthetic type II pyrethroid. Potent inhibitor of calcineurin (protein phosphatase 2B; IC_{50} = 2-4 nM). May also have varied effects on ion channels. Induces depolarization by keeping Na^+ channels in an open state.	25 mg

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Protein Phosphatase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Fostriecin, Sodium Salt, *Streptomyces pulveraceous*	**344280**	**(FST; Phosphotrienin)** An antitumor antibiotic that acts as a potent protein phosphatase 2A (PP2A) inhibitor (IC_{50} = 3.2 nM). Inhibits protein phosphatase 1 (PP1) at much higher concentrations (IC_{50} = 131 µM). Does not affect the activity of protein phosphatase 2B (PP2B). Inhibits the catalytic activity of DNA topoisomerase II (topo II) and arrests cell growth at the G_2/M phase of the cell cycle in a dose-dependent manner.	10 µg
ß-Glycerophosphate, Disodium Salt, Pentahydrate	**35675**	A phosphate group donor in matrix mineralization studies that acts as a protein phosphatase inhibitor. Accelerates calcification in vascular smooth muscle cells.	50 g 100 g 250 g
Microcystin-LF, *Microcystis aeruginosa*	**475814**	Analog of Microcystin-LR (Cat. No.475815) with Phe substituted in place of Arg. Believed to be more cell-permeable than other microcystins, making it useful for biochemical studies in intact cells. *Not available for sale outside the United States.*	25 µg
Microcystin-LR, *Microcystis aeruginosa*	**475815**	Cyclic heptapeptide toxin isolated from the freshwater cyanobacteria *Microcystis aeruginosa*. Potent inhibitor of protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A). Unlike Okadaic Acid (Cat. No.495604), microcystin-LR is effective on both PP1 (IC_{50} = 1.7 nM) and PP2A (IC_{50} = 40 pM). Reacts with phosphatase in a two-step mechanism involving rapid binding and inactivation of the catalytic subunit followed by slower covalent interactions. Has no effect on protein kinases, making it useful for reducing the effect of contaminating phosphatase activities in protein kinase assays. A 2.5 mM (250 µg/100 µl) solution of Microcystin-LR, *Microcystis aeruginosa* (Cat. No.475821) in DMSO is also available. *Not available for sale outside the United States.*	500 µg
InSolution™Microcystin-LR, *Microcystis aeruginosa*	**475821**	A 2.5 mM (250 µg/100 µl) of Microcystin-LR, *Microcystis aeurginosa* (Cat. No. 475815) in DMSO. *Not available for sale outside the United States.*	250 µg
Microcystin-LW, *Microcystis aeruginosa*	**475818**	Analog of Microcystin-LR (Cat. No.475815) with Trp substituted in place of Arg. Believed to be more cell-permeable than other microcystins making it useful for biochemical studies in intact cells. *Not available for sale outside the United States.*	25 µg
Microcystin-RR, *Microcystis aeruginosa*	**475816**	Arg-Arg analog of Microcystin-LR (Cat. No.475815) that is less toxic. Inhibits protein phosphatase 2A (IC_{50} = 3.4 nM). Useful for comparative structure and function studies. *Not available for sale outside the United States.*	250 µg
mpV(pic)	**475950**	A potent protein phosphotyrosine phosphatase inhibitor and insulin receptor kinase (IRK) activator. Excellent insulin mimetic *in vitro* and *in vivo*. Displays relative specificity as a phosphotyrosine phosphatase inhibitor by inhibiting insulin receptor dephosphorylation to a greater extent than epidermal growth factor receptor dephosphorylation.	10 mg
α-Naphthyl Acid Phosphate, Monosodium Salt	**479775**	Broad-spectrum protein phosphatase inhibitor.	5 g
NFAT Activation Inhibitor III	**480403**	**INCA-6; Inhibitor of NFAT-Calcineurin Association-6** A cell-permeable quinone compound that acts as a potent and selective inhibitor of Calcineurin-NFAT (Nuclear Factor of Activated T cells) signaling. Binds to calcineurin with high affinity (K_d = 800 nM), disrupts its interaction with NFAT and completely blocks its dephosphorylation, nuclear import of NFAT (~40 µM in C1.7W2 T cells), and induction of cytokine mRNAs. Unlike CsA (Cat. No.239835) and FK506, INCA-6 does not affect calcineurin activity or its downstream signaling.	5 mg
NIPP-1, His•Tag®, Bovine Thymus, Recombinant, *E. coli*	**482251**	**(Nuclear Inhibitor of Protein Phosphatase-1)** Recombinant, bovine NIPP-1 fused to a His•Tag® sequence and expressed in *E. coli*. Potent and specific inhibitor of 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. Also an ideal substrate for protein kinase A and casein kinase II. Thought to be involved in the targeting of PP1 to RNA-associated substrates and may also be involved in the dephosphorylation of transcription factors like CREB and the tumor suppressor Rb.	1 µg
InSolution™Nodularin, *Nodularia spumigena*	**488003**	**[NODLN; cyclo-(D-ß-Methyliso-Asp-L-Arg-Adda-D-iso-Glu-N-methyldehydrobutyrine; Adda = (2S,3S8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4(E),6(E)-decadienoic acid** A hepatotoxic cyclic pentapeptide that acts a potent and non-covalent-binding inhibitor of protein phosphatases PP2A and PP1 (IC_{50} = 33 pM and 1.6 nM, respectively, using phosphorylase a as the substrate) with no apparent effect on acid phosphatase, alkaline phosphatase, phosphorylase kinase, PKA, PKC, or IRTK. It inhibits PP2B with much less potency (IC_{50} = 8.7 µM) and shows little activity towards PP2C even at concentrations as high as 10 µM.	50 µg
InSolution™Okadaic Acid, *Prorocentrum concavum*	**495609**	A 250 µM (25 µg/124 µl) solution of Okadaic Acid, *Prorocentrum concavum* (Cat. No. 495604) in DMSO.	25 µg

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Protein Phosphatase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Okadaic Acid, Ammonium Salt	**459616**	Water-soluble analog of Okadaic Acid (Cat. No.495604). Inhibits protein phosphatases 1 and 2A.	25 µg
Okadaic Acid, Potassium Salt	**459618**	Water-soluble analog of Okadaic Acid (Cat. No.495604). Inhibits protein phosphatases 1 and 2A.	50 µg
Okadaic Acid, *Prorocentrum concavum*	**495604**	**(OA)** An ionophore-like polyether derivative of a C_{38} fatty acid compound that has tumor promoting properties. Potent inhibitor of protein phosphatase 1 (IC_{50} = 10-15 nM) and protein phosphatase 2A (IC_{50} = 0.1 nM). Does not affect the activity of tyrosine phosphatases, alkaline phosphatases, or acid phosphatases. Useful for the study of protein phosphatases in cell extracts as well as in intact cells. Induces apoptosis in human breast carcinoma cells (MB-231 and MCF7) and in myeloid cells but inhibits glucocorticoid-induced apoptosis in T cell hybridomas. Has marked contractile effects on smooth muscle and heart muscle. Implicated as causative agent of diarrhetic shellfish poisoning. A 250 µM (25 µg/124 µl) solution of Okadaic Acid, (Cat. No.495609) in DMSO is also available.	10 µg 25 µg 100 µg
Okadaic Acid, Sodium Salt	**459620**	Water-soluble analog of Okadaic Acid (Cat. No.495604). Inhibits protein phosphatases 1 and 2A.	25 µg
Phenylarsine Oxide	**521000**	**(Oxophenylarsine; PAO)** A membrane-permeable protein tyrosine phosphatase inhibitor (IC_{50} = 18 µM). Stimulates 2-deoxyglucose transport in insulin-resistant human skeletal muscle and activates $p56^{lck}$ protein tyrosine kinase. Blocks TNF-α-dependent activation of NF-κB in human myeloid ML-1a cells. PAO inhibits the protease activities of recombinant human caspases as well as endogenous caspases that are active in extracts of pre-apoptotic chicken DU249 cells (S/M extracts).	250 mg
PPM1D Phosphatase Inhibitor	**529578**	**2,5-*bis*-(2-Thienylidene)cyclopentanone** A cell-permeable thienylidene cyclopentanone compound that inhibits the PPM ser/thr phosphatase member PPM1D/PP2Cδ/WIP1 (IC_{50} = 8.4 µM), while exhibiting little activity against PPM1A even at concentrations as high as 100 µM. Selectively inhibits the growth of high PPM1D-expressing tumor cells (SF_{50} = 0.13, 0.17 & 0.48 µM for MCF-3B, KPL-1, & MCF-7, respectively, in colony formation assays), but not low PPM1D-expressing tumor cells (SF_{50} = 34 & >50 µM for 239T & HeLa, respectively). Inhibition of p38 MAP kinase activity by SB203580 (Cat. Nos.559389,559395, &559398) is shown to fully prevent PPM1D inhibitor-induced growth arrest of MCF-7 cells.	10 mg
PRL-3 Inhibitor	**539808**	**[1-(2-Bromobenzyloxy)-4-bromo-2-benzylidene rhodanine]** A cell-permeable benzylidene rhodanine compound that potently inhibits hPRL-3 (IC_{50} = 900 nM), a member of the regenerating liver family tyrosine phosphatases. Shown to reduce the invasiveness of murine melanoma B16F10 cells.	10 mg
Protein Phosphatase 2A Inhibitor I_2^{PP2A}, Human, Recombinant, *E. coli*	**539620**	**(I_2^{PP2A})** Recombinant, human PP2AI I_2 fused to GST and expressed in *E. coli*. Inhibits protein phosphatase 2A (PP2A) potently with K_i ~ 25-30 nM with myelin basic protein, histone H1, and other substrates of PP2A but not with casein as a substrate. Stimulates PP1. Prevents inhibition of E-Cdk-2 by $p21^{Cip1}$. Associates with B cyclin. Regulates histone binding to DNA, transcriptional activity and chromatin condensation. Undergoes phosphorylation in cells. Highly expressed in some cancers. Associates with HRX leukemia-associated fusion proteins. Occurs as fusion protein in acute undifferentiated leukemia. Does not inhibit PP1, PP2B, PP2C, or pyruvate dehydrogenase.	250 ng
Protein Phosphatase Inhibitor 2, Human, Recombinant, *E. coli*	**539638**	**(I-2; Inhibitor-2)** Recombinant, human PPI2 expressed in *E. coli*. Inhibitor-2 is the regulatory subunit of the cytosolic type 1 Ser/Thr protein phosphatase-1 (PP1). It potently inhibits the activity of the free catalytic subunit of PP1 (IC_{50} = 1 nM).	100 µg
Protein Phosphatase Inhibitor 2, Rabbit Muscle, Recombinant, *E. coli*	**539516**	**(PPI-2)** Recombinant, rabbit PPI2 expressed in *E. coli*. A 204-amino acid, heat-stable protein that specifically inhibits the catalytic subunit of protein phosphatase 1 (IC_{50} = 2 nM). Useful for distinguishing type 1 from type 2 protein phosphatases. A good substrate for CKI, CKII, GSK3ß, and PKA.	20 µg
Protein Tyrosine Phosphatase CD45 Inhibitor	**540215**	**[N-(9,10-Dioxo-9,10-dihydro-phenanthren-2-yl)-2,2-dimethyl-propionamide; PTPase CD45 Inhibitor]** A cell-permeable, potent, selective, competitive, and reversible inhibitor of CD45 (IC_{50} = 200 nM or 3.8 µM using *p*NPP or phosphorylated Ick^{505} peptide as a substrate, respectively). Does not effectively inhibit PTPIB (IC_{50} Ick^{505} peptide as a substrate). The phenanthrenedione group does not function as a thiol oxidizing agent.	1 mg

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Protein Phosphatase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Protein Tyrosine Phosphatase Inhibitor I	**540200**	**(α-Bromo-4-hydroxyacetophenone; 4-Hydroxyphenacyl Br)** A potent, cell-permeable, and covalent protein tyrosine phosphatase (PTP) inhibitor. Inhibits SHP-1 (ΔSH2), the catalytic domain of the SH2 domain-containing phosphatase SHP-1 (K_i = 43 µM), and PTPIB (K_i = 42 µM). The inhibition can be reversed by irradiation of the inactivated PTP at 350 nm.	10 mg
Protein Tyrosine Phosphatase Inhibitor II	**540205**	**(α-Bromo-4-methoxyacetophenone; 4-Methoxyphenacyl Br)** A potent, cell-permeable, and covalent protein tyrosine phosphatase (PTP) inhibitor. Binds to SHP-1 (ΔSH2), the catalytic domain of the SH2 domain-containing phosphatase SHP-1, with lower affinity than PTP Inhibitor I (Cat. No.540200) (K_i = 128 µM versus K_i = 43 µM) but with a higher k_{inact} (2.4 min^{-1} versus 0.4 min^{-1}). The inhibition can be reversed by irradiation of the inactivated PTP at 350 nm.	25 mg
Protein Tyrosine Phosphatase Inhibitor III	**540210**	**[α-Bromo-4-(carboxymethoxy)acetophenone; 4-(Carboxymethoxy)phenacyl Br]** A potent, cell-permeable, and covalent protein tyrosine phosphatase (PTP) inhibitor. Binds to SHP-1 (ΔSH2), the catalytic domain of the SH2 domain-containing phosphatase SHP-1, with lower affinity than PTP Inhibitor I (Cat. No.540200) (K_i = 193 µM versus K_i = 43 µM) but with a higher k_{inact} (1.8 min^{-1} versus 0.4 min^{-1}). The inhibition can be reversed by irradiation of the inactivated PTP at 350 nm.	10 mg
Protein Tyrosine Phosphatase Inhibitor IV	**540211**	**[*bis*(4-Trifluoromethylsulfonamidophenyl)-1,4-diisopropylbenzene]** An uncharged, 1,4-di-substituted, phenyl-linked *bis*-trifluoromethylsulfonamido (TFMS) phosphate mimetic that acts as a potent, reversible, competitive, and active-site directed inhibitor of protein tyrosine phosphatases (PTP; IC_{50} = 1.8, 2.5, 8.4, 13, 20, 6.4, and 6.7 µM for SHP-2, PTP1B, PTP-, PTP-Meg-2, PTP-σ, PTP-ß, and PTP-µ, respectively).	10 mg
PTP Inhibitor V, PHPS1	**540213**	**4-(N'-(3-(4-Nitrophenyl)-5-oxo-1-phenyl-1,5-dihydro-pyrazol-(4Z)-ylidene)-hydrazino)-benzenesulfonic acid** A cell-permeable phosphotyrosine mimetic that acts as a reversible, active-site targeting, substrate-competitive inhibitor of Shp-2 (IC_{50} and K_i = 2.1 and 0.73 µM, respectively). PHPS1 inhibits ECPTP, PTP1B, Shp1, mycobacterium MptpA only at higher concentrations (IC_{50} = 5.4, 19, 30, and 39 µM, respectively) and exhibits little activity against PTPH1, STEP, PTPN7, PTPRK, GLEPP1, or LAR2 even at concentrations as high as 50 µM. Shown to inhibit Shp-2-dependent cellular signaling and tumor cell colonies formation.	10 mg
PTP1B Inhibitor	**539741**	**[3-(3,5-Dibromo-4-hydroxy-benzoyl)-2-ethyl-benzofuran-6-sulfonicacid- (4-(thiazol-2-ylsulfamyl)-phenyl)-amide]** A cell-permeable sulfanamido-benzbromarone compound that acts as a selective, reversible and non-competitive allosteric inhibitor of PTP1B (IC_{50} = 4 µM and 8 µM for $PTP1B_{403}$ and $PTP1B_{298}$, respectively). Binds to a novel site away from the catalytic pocket and inhibits PTP1B activity by preventing closure of the WPD loop.	5 mg
RK-682, *Streptomyces* sp.	**557322**	**(3-Hexadecanoyl-5-hydroxymethyl-tetronic Acid)** A specific and noncompetitive inhibitor of protein tyrosine phosphatase with limited cell-permeability. Inhibits dephosphorylation activity of CD45 (IC_{50} = 54 µM) and VHR (vaccinia H1-related; IC_{50} = 2 µM) *in vitro*. Inhibits cell cycle progression of Ball-1 cells at the G_1/S transition and enhances ATP-induced long-term potentiation in guinea-pig hippocampal CA1 neurons.	200 µg
SHP1/2 PTPase Inhibitor, NSC-87877	**565851**	**[8-Hydroxy-7-(6-sulfonaphthalen-2-yl)diazenyl-quinoline-5-sulfonic acid, Disodium Salt]** A cell-permeable 7-aza-8-hydroxyquinoline compound that acts as a potent, catalytic site-targeting inhibitor of SHP-1 and SHP-2 protein tyrosine phosphatases (IC_{50} = 355 nM and 318 nM, respectively). It inhibits PTP1B and HePTP with less potency (IC_{50} = 1.69 µM and 7.75 µM, respectively) and exhibits >200-fold selectivity over DEP1, CD45, and LAR. Shown to inhibit both basal and stimulated SHP-2 activity in HEK293 cells.	50 mg
Sodium Orthovanadate	**567540**	A broad spectrum potent inhibitor of protein tyrosine phosphatases. Also known to inhibit Na^+,K^+-ATPase, acid and alkaline phosphatases, phosphofructokinase, and adenylate kinase. Also inhibits the ATPase activity of the reconstituted binding protein-dependent ATP-Binding Cassette (ABC) transporter for maltose ($MalFGK_2$) of *Salmonella typhimurium* in the micromolar range. Can be converted to pervanadate by hydrogen peroxide.	5 g
Sodium Stibogluconate	**567565**	**(Antimony Sodium Gluconate; $NaSb^v$; SSG)** A pentavalent antimony compound that irreversibly inhibits protein tyrosine phosphatase (PTPase) activity, including Src homology PTPase-1 (SHP-1) (99% inhibition at ~11 µM) by forming a stable complex. At higher concentrations (~110 µM), it inhibits SHP-2 and PTP1B activities.	1 g

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Protein Phosphatase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Suramin, Sodium Salt	**574625**	A reversible and competitive inhibitor of protein tyrosine phosphatases. An anti-neoplastic, anti-angiogenic agent that uncouples G-proteins from receptors presumably by blocking their interaction with intracellular receptor domains. Inhibits GDP-GTP exchange, the rate limiting step in the activation of G_{α}-subunits. A competitive inhibitor of reverse transcriptase. Reported to inhibit topoisomerases I and II. Inhibits Ca^{2+}-ATPase in sarcoplasmic reticulum membranes. Also inhibits the cell-surface binding of various growth factors, including EGF, PDGF, and TGF-ß. An inhibitor of phospholipase D (IC_{50} = 15 µM). Reported to interact with ATP-binding enzymes and P_2-purinergic receptors. An effective inhibitor of angiogenesis in the calmodulin assay when given in combination with angiostatic steroids.	50 mg 200 mg
Tautomycin, *Streptomyces spiroverticillatus*	**580551**	Mixture of two isomers. Potent inhibitor of protein phosphatases. Inhibits protein phosphatase 1 (IC_{50} = 1 nM), protein phosphatase 2A (IC_{50} = 10 nM), and smooth muscle endogenous phosphatase (IC_{50} = 6 nM). Higher concentrations are needed to inhibit protein phosphatase 2B. Does not inhibit protein phosphatase 2C.	50 µg

PROTEIN PHOSPHATASE INHIBITORS AND PHOSPHATASE INHIBITOR COCKTAILS

Phosphatase Inhibitor Cocktail Set I

A cocktail of three phosphatase inhibitors that will inhibit alkaline phosphatases as well as serine/threonine protein phosphatases such as PP1 and PP2A. This product is provided as a set of five 1 ml vials. Each vial contains 1 ml of phosphatase inhibitor cocktail solubilized in DMSO with the following components: Bromotetramisole oxalate (0.5 mM), Cantharidin (Cat. No. 210155; 500 µM), and Microcystin-LR (Cat. No. 475815; 500 nM). *Not available for sale outside the United States.*

Cat. No. 524624 — 1 set

Phosphatase Inhibitor Cocktail Set II

A cocktail of five phosphatase inhibitors for the inhibition of acid and alkaline phosphatases as well as protein tyrosine phosphatases (PTPs). Suitable for use with tissue and cell extracts, including extracts containing detergents. Provided as a set of five vials, with each vial containing 1 ml aqueous solution of 200 mM Imidazole, 100 mM Sodium Fluoride, 115 mM Sodium Molybdate, 100 mM Sodium Orthovanadate, and 400 mM Sodium Tartrate Dihydrate.

Cat. No. 524625 — 1 set

Phosphatase Inhibitor Cocktail Set III

A cocktail of four phosphatase inhibitors for the inhibition of both serine/threonine and protein tyrosine phosphatases. Available as a 1 ml vial or as a set of five 1 ml vials. Each vial contains 1 ml of aqueous solution with the following components: 50 mM Sodium Fluoride, 10 mM β-Glycerophosphate, 10 mM Sodium Pyrophosphate Decahydrate, and 1 mM Sodium Orthovanadate.

Cat. No. 524627 — 1 ml
1 set

Phosphatase Inhibitor Cocktail Set IV

A cocktail of three phosphatase inhibitors for the inhibition of both serine/threonine and alkaline phosphatases. Available as a 1 ml vial or as a set of five 1 ml vials. Each vial contains 1 ml of solution with the following components: 500 µM Cantharidin (Cat. No. 210155), 2.5 mM (-)-*p*-Bromotetramisole oxalate, and 1 µM Calyculin A, *Discodermia calyx* (Cat. No. 208851).

Cat. No. 524628 — 1 ml
1 set

Phosphatase Inhibitor Cocktail Set 5, 50X

A cocktail of four phosphatase inhibitors for the inhibition of both serine/threonine and protein tyrosine phosphatases. Available as 1 ml or as a set of five 1 ml vials. Each vial contains 1 ml of aqueous solution with the following components: 250 mM Sodium Fluoride, 50 mM ß-Glycerophosphate (Cat. No. 35675), 50 mM Sodium Pyrophosphate Decahydrate, 50 mM Sodium Orthovanadate.

Cat. No. 524629 — 1 ml
1 set

Phosphotyrosine Phosphatase Inhibitor Set (Vanadium)

Contains 5 g of Sodium Orthovanadate (Cat. No. 567540), 10 mg each of bpV(phen) (Cat. No. 203695) and mpV(pic) (Cat. No. 475950).

Cat. No. 525325 — 1 set

Protein Phosphatase Inhibitor Set II

Contains 10 mg Cypermethrin (Cat. No, 239900), 1 mg Dephostatin (Cat. No. 263200), 10 µg Okadaic Acid (Cat. No. 495604), and 1 µg NIPP-1, Bovine Thymus.

Cat. No. 539630 — 1 set

AMP-Activated Protein Kinase (AMPK)

5'-AMP-activated protein kinase (AMPK), a trimeric enzyme in mammals, consists of a catalytic α subunit (63 kDa) and the non-catalytic ß and γ subunits. The N-terminal of the α subunit contains a serine/threonine kinase catalytic domain. The ß and γ subunits interact with the C-terminal region of the α subunit. There are two genes that encode isoforms of both the α and ß subunits (α1, α2, ß1 and ß2) and three genes encode isoforms of the γ subunit (γ1-γ3). The α2 isoform is found predominantly in skeletal and cardiac muscle. Hepatic tissue exhibits an equal distribution of both α1 and α2 isoforms, and in pancreatic ß-cells largely the α1 is expressed.

AMPK is activated by increases in the cellular AMP/ATP ratio caused by metabolic stress that either interfere with ATP production or accelerates ATP consumption. AMP affects AMPK by a direct allosteric activation thereby making it a poor substrate for dephosphorylation. Even a small increase in AMP levels can induce a significant increase in the activity of AMPK. AMPK is activated by phosphorylation at Thr^{172} in the activation loop by one or more upstream AMPK kinases, including Akt. LKB1, an upstream constitutively active protein kinase, phosphorylates AMPK when AMP levels are elevated in cells. In addition, Ca^{2+}/CaM kinase ß is shown to phosphorylate and activate AMPK when calcium levels are increased, independent of any increase in AMP levels.

AMPK stimulates pathways that are linked to increased energy production, such as glucose transport and fatty acid oxidation. On the other, hand it switches off the energy consuming pathways, such as lipogenesis, protein synthesis, and gluconeogenesis.

References:
Towler, M.C., and Hardie, D.G. 2007. *Circ. Res.* **100,** 328.
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AMPK Inhibitors

Product	Cat. No.	Comments	Size
AMPK Inhibitor, Compound C	**171260**	A cell-permeable pyrrazolopyrimidine compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of AMPK (AMP-activated protein kinase; K_i = 109 nM in the presence of 5 µM ATP and the absence of AMP). Does not affect the activities of ZAPK, Syk, PKCθ, PKA, or JAK3. Blocks cellular activities induced by AICAr (Cat. No.123040) or Metformin (Cat. No.317240). Induces weight loss by attenuating AMPK-mediated food intake in mice. A 10 mM (1 mg/250 µl) solution of AMPK Inhibitor, Compound C (Cat. No.171261) in DMSO is also available.	1 mg 5 mg
InSolution™AMPK Inhibitor, Compound C	**171261**	A 10 mM (1 mg/250 µl) solution of AMPK inhibitor, compound C (Cat. No. 171260) in DMSO.	1 mg
STO-609	**570250**	A cell-permeable and reversible naphthoyl fused benzimidazole compound that acts as a highly selective, potent, ATP-competitive inhibitor of Ca^{2+}/calmodulin-dependent protein kinase kinase (CaM-KK) [IC_{50} = 120 ng/ml and 40 ng/ml for CaM-KKα and CaM-KKß 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} = ~10 µg/ml), CaM-KI, CaM-KIV, PKA, PKC, and p42 MAP kinase (IC_{50} >10 µg/ml). Has also been reported to inhibit phosphorylation of AMP-activated protein kinase (AMPK).	5 mg

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Aurora Kinase Inhibitors

Product	Cat. No.	Comments	Size
Aurora Kinase Inhibitor III	**189405**	**[Cyclopropanecarboxylic acid-(3-(4-(3-trifluoromethyl-phenylamino)-pyrimidin-2-ylamino)-phenyl)-amide]** A cell-permeable 2,4-dianilinopyrimidine compound that acts as an ATP-competitive, potent, but non-selective inhibitor of Aurora A (IC_{50} = 42 nM). At higher concentrations, also inhibits the activities of other kinases, such as Lck, Bmx, IGF-1R, and Syk (IC_{50} = 131, 386, 591, and 887 nM, respectively).	1 mg
Aurora Kinase/Cdk Inhibitor	**189406**	**{4-(5-Amino-1-(2,6-difluorobenzoyl)-1H-[1,2,4] triazol-3-ylamino)-benzenesulfonamide}** A cell-permeable triazolylsulfonamido compound that acts a reversible, ATP-competitive kinase inhibitor with selectivities towards Aurora kinases (IC_{50} = 11 and 15 nM for Aurora-A, Aurora-B, respectively) and Cdk's (IC_{50} = 9, 4, and 3 nM for Cdk1/B, Cdk2/A, and Cdk2/E, respectively). Displays antitumor properties both *in vitro* (IC_{50} in the range of 112 - 514 nM against various human cancer cell lines) and in a xenograft murine model *in vivo* (75-100 mg/kg, i.p.).	5 mg
4-(4'-Benzamidoanilino)-6,7-dimethoxyquinazoline	**189404**	**4-(4'-Benzamidoanilino)-6,7-dimethoxyquinazoline** A cell-permeable anilinoquinazoline compound that acts as a potent, selective, and ATP-competitive inhibitor of Aurora kinases (IC_{50} = 310 nM and 240 nM for Aurora A and B, respectively, 1.25 µM in MCF7 cells). Due to its limited aqueous solubility and high serum binding property, it is recommended for *in vitro*, but not *in vivo*, use.	1 mg
Binucleine 2	**201125**	**N'-(1-(3-Chloro-4-fluorophenyl)-4-cyano-1H-pyrazol-5-yl)-N,N-dimethyliminoformamide** A cell-permeable pyrazolo compound that inhibits cytokinesis function of the Aurora B kinase pathway. Inhibits Histone H3 phosphorylation on Ser^{10} in mitotic *Drosophila* Kc167 cells at 20 µM, while inactive in mammalian systems. Does neither function as a general kinase inhibitor nor inhibit Cdk-dependent entry into mitosis.	5 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). The α and β isoforms are most abundant in neurons, whereas δ or γ isoforms are expressed in most tissues. The δ isoform is the most prominent isoform in cardiomyocytes. 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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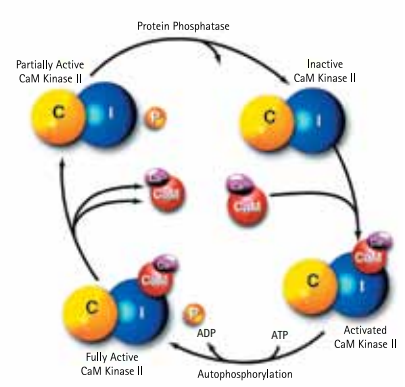

Calmodulin-Dependent Protein Kinase (CaM Kinase) Inhibitors

Product	Cat. No.	Comments	Size
[Ala286]-Ca^{2+}/Calmodulin Kinase II Inhibitor 281-301	**208710**	**(CaM Kinase II Inhibitor 281-301; MHRQEAVDCLKKFNARRKLKG-NH_2)** A synthetic peptide corresponding to residues 281-301 of the CaM kinase II α-subunit. Acts as a potent inhibitor of CaM kinase II catalytic fragment (IC_{50} = 2 µM). The inhibition is competitive with respect to ATP and noncompetitive with respect to peptide substrate.	500 µg
Autocamtide-2 Related Inhibitory Peptide	**189480**	**[(Ala^9)-Autocamtide-2; AIP; KKALRRQEAVDAL]** Non-phosphorylatable analog of Autocamtide-2 (Cat. No.189475) that acts as a highly specific and potent inhibitor of calmodulin-dependent protein kinase II (IC_{50} = 40 nM). It is about 50 times more potent than [Ala^{286}]-CaM kinase II Inhibitor, 281-301 (Cat. No.208710). Has no effect on PKA, PKC, and CaM kinase IV. Blocks Ca^{2+}-induced insulin secretion from electropermeabilized islets.	500 µg
Autocamtide-2 Related Inhibitory Peptide II	**189484**	**(A3K/V10F-AIP; AIP-II; KKKLRRQEAFDAL)** An AIP (Cat. No. 189480) analog, in which Ala^3 and Val^{10} are replaced with Lys and Phe respectively. Acts as a highly specific, potent inhibitor of calmodulin-dependent protein kinase II (CaMKII; IC_{50} = 4.1 nM). Displays ~10-fold greater potency than AIP. Inhibits PKC at higher concentrations (IC_{50} = 1 µM) and does not affect the activities of CaMK IV and PKA (IC_{50} > 100 µM).	1 mg
Autocamtide-2 Related Inhibitory Peptide II, Cell-permeable	**189485**	**(Ac-RQIKIWFQNRRMKWKKKKKLRRQEAFDAL-OH; Ant-A3K/V10F-AIP; Ant-AIP-II)** A highly specific, potent, cell-permeable calmodulin-dependent protein kinase II (CaMKII) inhibitor that contains the *Antennapedia* transport peptide sequence fused to the amino terminus of AIP-II (Cat. No.189484).	1 mg
Autocamtide-2 Related Inhibitory Peptide, Myristoylated	**189482**	**(Myr-N-KKALRRQGAVDAL-OH; Myristoylated AIP)** This peptide corresponds to AIP (Cat. No.189480) which has been myristoylated at the N-terminus, thus enhancing its cell-permeability.	500 µg

Calmodulin-Dependent Protein Kinase (CaM Kinase) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Ca^{2+}/Calmodulin Kinase II Inhibitor 281-309	**208711**	**(CaM Kinase II Inhibitor 281-309; MHRQETVDCLKKFNARRKLKGAILTTMLA-OH)** A synthetic peptide that contains the CaM-binding, inhibitory, and autophosphorylation domains of CaM kinase II. Can be phosphorylated at Thr^{286} by PKC. Useful as a calmodulin binding peptide. Inhibits CaM kinase II (IC_{50} = 80 nM) by blocking Ca^{2+}/calmodulin activation and enzyme active site (IC_{50} = 2 µM).	500 µg
Calmodulin Binding Domain	**208734**	**(Calmodulin antagonist; CaM kinase II 290-309)** Potent calmodulin antagonist. Inhibits activation of calmodulin-dependent protein kinase II (IC_{50} = 52 nM). Interacts with the catalytic core of CaM kinase II as a pseudosubstrate.	1 mg
Calmodulin Kinase IINtide	**208920**	**(KRPPKLGQIGRAKRVVIEDDRIDDVLK-OH)** A potent and specific inhibitor of CaMK II (IC_{50} = 50 nM for both the total and Ca^{2+}-independent CaMK II activity). Exhibits inhibitory activity across converged species, including rat brain, goldfish brain, and *Drosophila* (IC_{50} range 100-400 nM). Does not affect the activities of CaMK I, CaMK IV, CaMKK, PKA, or PKC. The peptide sequence corresponds to the inhibitory domain of CaMK IIN.	1 mg
Calmodulin Kinase IINtide, Myristoylated	**208921**	**(Myr-N-GGGKRPPKLGQIGRAKRVVIEDDRIDDVLK-OH)** The myristoylated form of CaMK IINtide (Cat. No.208920). The peptide has been modified at the amino terminal lysine with the addition of three glycine residues and myristoylated to improve cell-permeability.	1 mg
CaMKII Inhibitor	**208922**	**[CK59; 2-(2-Hydroxyethylamino)-6-aminohexylcarbamic acid tert-butyl ester-9-isopropylpurine]** A cell-permeable Olomoucine (Cat. Nos.495620 &495624) analog that acts as a CaMKII inhibitor (IC_{50} 50 ≤5 µM) and GLUT4 membrane translocation (IC_{50} = 100 µM) in 3T3-L1 adipocytes.	5 mg
H-89, Dihydrochloride	**371963**	**{N-[2-((*p*-Bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 2HCl}** A cell-permeable, selective, reversible, ATP-competitive and potent inhibitor of protein kinase A (K_i = 48 nM). Inhibits other kinases only at much higher concentrations: CaM kinase II (K_i = 29.7 µM), casein kinase I (K_i = 38.3 µM), myosin light chain kinase (K_i = 28.3 µM), protein kinase C (K_i = 31.7 µM), and ROCK-II (IC_{50} = 270 nM). May be used to discriminate between the effects of PKA and cAMP-regulated guanine-nucleotide-exchange factors (GEFs) such as GEFI, GEFII, or Epac (exchange protein directly activated by cAMP). Enhances radiation-induced apoptosis in the human cell line BM 13674. A 10 mM (1 mg/193 µl) solution of H-89, 2HCl (Cat. No.371962) in DMSO is also available.	1 mg
HA 1004, Dihydrochloride	**371964**	**[N-(2-Guanidinoethyl)-5-isoquinolinesulfonamide, 2HCl]** A cell-permeable, reversible, and ATP-competetive inhibitor of protein kinase A (K_i = 2.3 µM), CaM kinase II (K_i = 13 µM), myosin light chain kinase (K_i = 150 µM), protein kinase C (K_i = 40 µM), and protein kinase G (K_i = 1.3 µM). An intracellular Ca^{2+} antagonist with no effect on cardiac function. Causes selective pulmonary vasodilation during pulmonary hypertension.	1 mg
InSolution™K-252a, *Nocardiopsis* sp.	**420297**	A 1 mM (100 µg/214 µl) solution of K-252a (Cat. No. 420298) in anhydrous DMSO.	100 µg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable, reversible, and ATP-competitive inhibitor against multiple protein kinases, including, but not limited to, CaM kinase II (K_i = 1.8 nM), myosin light chain kinase (K_i = 20 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), protein kinase G (K_i = 20 nM), NGF receptor $gp140^{trk}$ (IC_{50} = 3 nM), its transforming *trk* oncogenes, and the related neurotrophin receptors $gp145^{trkB}$ and $gp145^{trkC}$. Reported to induce apoptosis and cell cycle arrest by decreasing Cdk1 and Cdc25c activity in T98G cells and inhibit Flt3 phosphorylation in Flt3/Itd-BaF3 cells (IC_{50} <50 nM). Also available as a premade 1 mM (100 µg/214 µl) solution in DMSO (Cat. No.420297).	100 µg
KN-62	**422706**	**{1-[N,O-*bis*-(5-Isoquinolinesulfonyl)-N-methyl-L-tyrosyl]-4-phenylpiperazine}** A cell-permeable, reversible, and selective inhibitor of CaM kinase II (K_i = 900 nM for rat brain CaM kinase II) that binds directly to the calmodulin binding site of the enzyme. Also inhibits the growth of K562 cells in a dose-dependent manner.	1 mg
KN-92	**422709**	**{2-[N-(4-Methoxybenzenesulfonyl)]amino-N-(4-chlorocinnamyl)-N-methylbenzylamine, Phosphate}** Useful as a negative control for KN-93 (Cat. No.422708), a Ca^{2+}/CaM kinase II inhibitor.	1 mg
KN-93	**422708**	**{2-[N-(2-hydroxyethyl)]-N-(4-methoxybenzenesulfonyl)] amino-N-(4-chlorocinnamyl)- N-methylbenzylamine)}** A cell-permeable, reversible and 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 CaMKII. Has no significant effects on protein kinase A activity. Induces G_1 cell cycle arrest and apoptosis in NIH/3T3 cells. A 5 mM (1 mg/399 µl) solution of KN-93 (Cat. No.422712) in DMSO is also available.	1 mg 5 mg
InSolution™KN-93	**422712**	A 5 mM (1 mg/399 µl) solution of KN-93 Inhibitor (Cat. No. 422708) in DMSO.	1 mg

Calmodulin-Dependent Protein Kinase (CaM Kinase) Inhibitors *continued*

Product	Cat. No.	Comments	Size
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**	**[Compound 5; 5-(N-2',5'-Dihydroxybenzyl)aminosalicylic Acid]** A cell-permeable, reversible, substrate competitive, and potent inhibitor of $pp60^{c\text{-}src}$ (IC_{50} = 200 nM) and CaM kinase II (IC_{50} = 200 nM).	1 mg
PP1 Analog II, 1NM-PP1	**529581**	A cell-permeable and reversible PP1 analog (Cat. No.529579) that acts as a potent and selective ATP-competitive inhibitor of mutant kinases over wild-type (IC_{50} = 3.2 nM for T339G, c-Fyn-as1 vs. 1.0 µM for c-Fyn; 4.3 nM for I338G, v-src-as1 vs. 28 µM for v-src; 5 nM for F80G, CDK2-as1 vs. 29 µM for CDK2; 8 nM for F89G, CAMK IIα-as1 vs. 24 µM for CAMKII; 120 nM for T315A, c-Abl-as2 vs. 3.4 µM for c-Abl). Shown to activate mutants of Ire1, a transmembrane kinase.	1 mg
STO-609	**570250**	A cell-permeable and reversible naphthoyl fused benzimidazole compound that acts as a highly selective, potent, ATP-competitive inhibitor of Ca^{2+}/calmodulin-dependent protein kinase kinase (CaM-KK) [IC_{50} = 120 ng/ml and 40 ng/ml for CaM-KKα and CaM-KKß 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} = ~10 µg/ml), CaM-KI, CaM-KIV, PKA, PKC, and p42 MAP kinase (IC_{50} >10 µg/ml). Has also been reported to inhibit phosphorylation of AMP-activated protein kinase (AMPK).	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. CKI substrates include transcription factors, cytoskeleton proteins, receptors, tau proteins, presenilin, and β-catenin. 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.

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Casein Kinase (CK) Inhibitors

Product	Cat. No.	Comments	Size
A3, Hydrochloride	**100122**	**[N-(2-Aminoethyl)-5-chloronaphthalene-1-sulfonamide, HCl]** A cell-permeable, reversible, and shorter alkyl chain derivative of W-7 that inhibits casein kinase I (K_i = 80 µM), casein kinase II (K_i = 5.1 µM), myosin light chain kinase (K_i = 7.4 µM), protein kinase A (K_i = 4.3 µM), protein kinase C (K_i = 47 µM), and protein kinase G (K_i = 3.8 µM).	10 mg
Casein Kinase I Inhibitor, D4476	**218696**	**{CKI Inhibitor; 4-(4-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-5-pyridin-2-yl-1H-imidazol- 2-yl)benzamide}** A cell-permeable triaryl substituted imidazolo compound that acts as a potent, reversible and relatively specific ATP-competitive inhibitor of CK1 (IC_{50} = 0.2 µM from *S. pombe*; 0.3 µM for CK1δ) and ALK5 (IC_{50} = 0.5 µM). A weak inhibitor of p38α MAP kinase (IC_{50} = 12 µM) and only weakly affects the activities of a panel of kinases tested, including PKB, SGK and GSK-3ß. Suppresses the site-specific phosphorylation (Ser^{322} and Ser^{325}) and nuclear exclusion of FOXO1a in H4IIE hepatoma cells. Shown to be ~10-fold more potent than IC261 (Cat. No.400090; IC_{50} = 2.5 µM for CK1).	1 mg
InSolution™Casein Kinase I Inhibitor, D4476	**218705**	A 10 mM (1 mg/251 µl) solution of Casein Kinase I Inhibitor, D4476 (Cat. No. 218696) in DMSO.	1 mg
Casein Kinase II Inhibitor I	**218697**	**(CKII Inhibitor; TBB; TBBt; 4,5,6,7-Tetrabromo-2-azabenzimidazole; 4,5,6,7-Tetrabromobenzotriazole)** A cell-permeable benzotriazolo compound that acts as a higly selective, reversible, and ATP/GTP-competitive inhibitor of casein kinase-2 (CK2) (IC_{50} = 900 nM and 1.6 µM, using rat liver and human recombinant CK2, respectively) and DYRK (IC_{50} 50 = 20 and 60 µM, using DNA and RNA substrate, respectively) and WNV (IC_{50} = 1.7 and 900 nM, using DNA and RNA substrate, respectively). A 10 mM (5 mg/1.15 ml) solution of Casein Kinase II Inhibitor I (Cat. No.218708) in DMSO, is also available.	10 mg
InSolution™Casein Kinase II Inhibitor I	**218708**	A 10 mM (5 mg/1.15 ml) solution of Casein Kinase II Inhibitor I (Cat. No. 218697) in DMSO.	5 mg
Casein Kinase II Inhibitor III, TBCA	**218710**	**[CKII Inhibitor, TBCA; (E)-3-(2,3,4,5-Tetrabromophenyl)acrylic acid]** A cell-permeable tetrabrominated cinnamic acid compound that acts as a potent and ATP-competitive inhibitor of Casein Kinase II (IC_{50} = 110 nM, K_i = 77 nM) with greater selectivity than TBB (Cat. Nos.218697 and218708) and DMAT (Cat. Nos.218699 and218706) against a panel of 28 commonly studied kinases. Shown to efficiently induces apoptosis in Jurkat cells (DC_{50} = 7.7 µM).	5 mg
Casein Kinase II Inhibitor IV	**218714**	**5-Oxo-5,6-dihydroindolo[1,2-a]quinazoline-7-acetic acid** A cell-permeable indoloquinazolinone compound that acts as a potent and selective CK2 inhibitor (IC_{50} = 390 nM with 100 µM ATP) in an ATP- and GTP-competitive manner (K_i = 0.17 and 0.21 µM, respectively). IQA exhibits much reduced activity against PI 3-Kα/ß/γ (No inhibition at 20 µM) and 48 commonly studied protein kinases (IC_{50} ≥10 µM with 100 µM ATP) and is more selective than TBB (Cat. Nos. 218697 and 218708) with respect to DYRK1a (IC_{50} = 8 and <1 µM, respectively, with 100 µM ATP).	5 mg
Daidzein	**251600**	**(4',7-Dihydroxyisoflavone)** Inactive analog of Genistein (Cat. No.345834). Blocks the G_1 phase of the cell cycle in Swiss/3T3 cells by inhibiting casein kinase II activity. Inhibits the growth of MiaPaC-2 and PANC-1 cells (IC_{50}= 45 µM and 75 µM, respectively).	25 mg
5,6-Dichloro-1-β-D-ribofuranosylbenz–imidazole	**287891**	**(5,6-Dichlorobenzimidazole Riboside; DRB)** A potent, ATP-competitive, and specific inhibitor of casein kinase II (IC_{50} = 6 µM). Reported to inhibit insulin-stimulated nuclear and cytosolic p70S6 kinase in CHO cells. Accentuates premature termination of transcription. Has been used to inhibit RNA polymerase II transcription which may be dependent on casein kinase II. Inhibits germinal vesicle breakdown in bovine oocytes. Induces G_1/S cell cycle arrest.	50 mg
Ellagic Acid, Dihydrate	**324683**	**4,4',5,5',6,6'-Hexahydroxydiphenic Acid 2,6,2',6'-Dilactone** A cell-permeable, reversible, potent antioxidant that has anti-mutagenic and anti-carcinogenic properties. Acts as a selective and ATP-competitive inhibitor of CK2 (IC_{50} = 40 nM). Moderately inhibits DNA topoisomerases I and II, Lyn, PKA catalytic subunit, Lyk, GSK-3, PKC, and FGR (IC_{50} = 1.8, 2.1, 2.9, 3.5, 4.3, 7.5, 8.0, and 9.4 µM, respectively). Only minimally inhibits DYRK1a, CSK, RET, Flt3, and NPM-ALK (IC_{50} >40 µM). Shown to act as an uncompetitive inhibitor of arginine methyltransferase CARM1 and block histone H3R17 methylation.	500 mg
InSolution™H-89, Dihydrochloride	**371962**	**N-[2-((*p*-Bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 2HCl** A 10 mM (1 mg/193 µl) solution of H-89, Dihydrochloride (Cat. No. 371963) in DMSO. *Not available for sale in Japan.*	1 mg

Casein Kinase (CK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
H-89, Dihydrochloride	**371963**	**{N-[2-((*p*-Bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 2HCl}** A cell-permeable, selective, reversible, ATP-competitive and potent inhibitor of protein kinase A (K_i = 48 nM). Inhibits other kinases only at much higher concentrations: CaM kinase II (K_i = 29.7 µM), casein kinase I (K_i = 38.3 µM), myosin light chain kinase (K_i = 28.3 µM), protein kinase C (K_i = 31.7 µM), and ROCK-II (IC_{50} = 270 nM). May be used to discriminate between the effects of PKA and cAMP-regulated guanine-nucleotide-exchange factors (GEFs) such as GEFI, GEFII, or Epac (exchange protein directly activated by cAMP). Enhances radiation-induced apoptosis in the human cell line BM 13674. A 10 mM (1 mg/193 µl) solution of H-89, 2HCl (Cat. No.371962) in DMSO is also available.	1 mg
Hypericin	**400076**	Polycyclic dione that has anti-retroviral activity. Inhibits protein kinase C (IC_{50} = 3.3 µM). Also known to inhibit casein kinase II (IC_{50} = 6 nM), MAP kinase (IC_{50} = 4 nM), and the protein tyrosine activities of the insulin receptor (IC_{50} = 20-29 nM) and the epidermal growth factor receptor (IC_{50} = 35 nM).	1 mg
IC261	**400090**	**{3-[(2,4,6-Trimethoxyphenyl)methylidenyl]-indolin-2-one}** A cell-permeable, reversible, potent and selective inhibitor of casein kinase (CK1) that inhibits CK1δ (IC_{50} = 0.7-1.3 µM) and CK1 (IC_{50} = 0.6-1.4 µM) isozymes. Also inhibits CK1α_1 at much higher concentrations (IC_{50} = 11-21 µM). The inhibition is competitive with respect to ATP. Only weakly inhibits PKA, $p34^{cdc2}$, and $p55^{fyn}$ (IC_{50}s > 100 µM). At low micromolar concentrations, IC261 inhibits cytokinesis causing a transient mitotic arrest.	5 mg

eEF-2 Kinase Inhibitors

Product	Cat. No.	Comments	Size
eEF-2 Kinase Inhibitor, NH125	**324515**	**(CaM-Dependent Kinase III Inhibitor, NH125; 1-Benzyl-3-cetyl-2-methylimidazolium iodide; 1-Cetyl-3-benzyl-2-methylimidazolium iodide)** A cell-permeable imidazolium compound that inhibits the activity of bacterial histidine kinases (EnvZ, PhoQ, BvgS, and EvgS) and eukaryotic eEF-2 (elongation factor 2) kinase/CaMKIII (IC_{50} = 60 nM), while exhibiting much lower potency against PKC, PKA, and CaMKII (IC_{50} = 7.5, 80, and >100 µM, respectively). NIH125 is a known P-gp substrate, which limits its *in vivo* efficacy as an anticancer and antimicrobial agent.	5 mg
TX-1918	**655203**	**2-((3,5-dimethyl-4-hydroxyphenyl)-methylene)-4-cyclopentene-1,3-dione** A cell-permeable arylidene-cyclopentenedione derived tyrphostin that acts as a potent inhibitor for eEF2-K (IC_{50} = 440 nM), while it inhibits other kinases at much higher concentrations (IC_{50} = 4.4, 44, 44, and 440 µM for Src, PKA, PKC, and EGFR-K, respectively). Displays potent antitumor activity (EC_{50} = 2.07 and 230 µM in HepG2 and HCT116 tumor cells, respectively) with greatly reduced mitochondrial- (≥5000-fold) and hepato-toxicity (≥90-fold) when compared with another tyrphostin, AG 17 (Cat. No.658425). It is therefore a more promising candidate as a therapeutic agent for cancer treatment.	10 mg

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Glycogen Synthase Kinase-3 (GSK-3) Inhibitors

Glycogen synthase kinase-3 (GSK-3), a multifunctional serine/threonine kinase, is a key regulator of numerous signaling pathways. Two isoforms of GSK-3 are reported in mammals: a 51 kDa GSK-3α and a 47 kDa GSK-3β. GSK-3β is constitutively active in resting cells and treatment of cells with an agent, such as insulin, is shown to cause GSK-3 inactivation through a PI 3-kinase (PI 3-K)-dependent mechanism. PI 3-K-induced activation of PKB/Akt results in phosphorylation of Ser^{21} on GSK-3α and Ser^{9} on GSK-3β, which inhibits GSK-3 activity. The phosphorylated N-terminus becomes a primed pseudosubstrate that occupies the positive binding pocket and the active site of the enzyme and acts as a competitive inhibitor for true substrates. This prevents phosphorylation of substrates. Arg^{96} is shown to be a crucial component of the positive pocket that binds primed substrates. Small molecule inhibitors that fit in the positively charged pocket of the kinase domain of GSK-3β are useful for selectively inhibiting primed substrates. Several known GSK-3 substrates participate in a wide spectrum of cellular processes, including glycogen metabolism, transcription, translation, cytoskeletal regulation, intracellular vesicular transport, cell cycle progression, and apoptosis. Phosphorylation of these substrates by GSK-3β usually has an inhibitory effect.

Abnormalities in pathways that use GSK-3 as a regulator have been linked to several disease conditions. Hence, GSK-3 has emerged as a potential therapeutic target, particularly in non-insulin-dependent diabetes mellitus, Alzheimer's disease, developmental disorders, and cancer. Several new GSK-3 inhibitors have recently been developed, most of which act in an ATP competitive manner. Inhibitors belonging to aloisines, the paullones, and the maleimide families, have shown promise as therapeutic agents. Due to its involvement in multiple pathways, selectivity of GSK-3 inhibition is an important factor in the development of inhibitors for therapeutic applications.

Glycogen Synthase Kinase Inhibitors

Product	Cat. No.	Comments	Size
1-Azakenpaullone	**191500**	A Kenpaullone (Cat. No.422000) analog that acts as a potent and ATP-competitive inhibitor of GSK-3ß (IC_{50} = 18 nM), and displays ~100-200 fold greater selectivity over Cdk1/B and Cdk5/p25 (IC_{50} = 2 µM and 4.2 µM, respectively).	1 mg
Aloisine A	**128125**	**{7-*n*-Butyl-6-(4-hydroxyphenyl)[5H]pyrrolo[2,3-b]pyrazine; RP107}** A cell-permeable pyrrolo-pyrazine compound that exerts anti-proliferative effects. Acts as a potent, selective, reversible, and ATP-competitive inhibitor of cyclin-dependent kinases (Cdks; IC_{50} = 150 nM, 120 nM, 400 nM, and 200 nM for Cdk1/cyclin B, Cdk2/cyclin A, Cdk2/cyclin E, and Cdk5/p25, respectively), glycogen synthase kinase-3 (GSK-3; IC_{50} = 500 nM and 1.5 µM for GSK-3α, GSK-3ß, respectively), and c-Jun N-terminal kinase (JNK; IC_{50} = ~ 3 - 10 µM). It inhibits several other enzymes (CK1, CK2, MAPKK, PKA, PKG, PKCs, and c-raf) poorly (IC_{50} ≥ 100 µM). Shown to arrest cells in both G_1 and G_2 phases (IC_{50} = 7 µM and 10.5 µM for undifferentiated human teratocarcinoma cells NT2 and differentiated postmitotic neurons hNT, respectively). Shown to selectively stimulate CFTR-dependent iodide efflux in wtCFTR-CHO, Calu-3 and F508del-CFTR-CF15 cells in the presence of 1 µM Forskolin (Cat. No.344270) with high affinity (EC_{50} = 150 nM, 140 nM and 111 nM, respectively).	5 mg
Aloisine, RP106	**128135**	**{7-*n*-Butyl-6-(4-methoxyphenyl)[5H]pyrrolo[2,3-b]pyrazine; RP106}** A cell-permeable pyrrolo-pyrazine compound that exerts anti-proliferative effects. Acts as a potent, selective, ATP-competitive inhibitor of CDK1/cyclin B, CDK5/p25, and GSK-3 (IC_{50} = 700 nM, 1.5 µM, and 920 nM, respectively).	5 mg
Alsterpaullone	**126870**	**{9-Nitro-7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one}** A cell-permeable, potent, reversible, and ATP competitive inhibitor of GSK-3ß (IC_{50} = 4 nM) and Cdk1/cyclin B (IC_{50} = 35 nM). Displays remarkable *in vitro* antitumor activity. Inhibits Tau phosphorylation at sites that are typically phosphorylated by GSK-3ß in Alzheimer's disease. Also inhibits Cdk5/p25-dependent phosphorylation of DARPP-32.	1 mg
Alsterpaullone, 2-Cyanoethyl	**126871**	A cell-permeable and reversible Alsterpaullone (Cat. No.126870) derivative that acts as a highly potent, ATP-competitive, selective inhibitor of Cdk1/cyclin B and GSK-3ß (IC_{50} = 230 pM and 800 pM, respectively; [ATP] = 15 µM). Displays ~37-fold greater selectivity for Cdk1/cyclin B over Cdk5/p25 (IC_{50} = 30 nM). Shown to inhibit other kinases in a commercially available testing screen panel (pIC_{50} = $-\log IC_{50}$[M]; pIC_{50} = ~ 7.5, 7.0, 7.0, 6.5, 6.5, 6.0, and 6.0 for Cdk2/A, Cdk4/D1, GSK-3ß, PDGFRß, Src, VEGFR-2, and VEGFR-3, respectively; [ATP] = 1 µM).	1 mg
Cdk1/2 Inhibitor III	**217714**	A cell-permeable triazolo-diamine compound that displays anti-proliferative properties in various human cancer cells (IC_{50} = 20 nM, 35 nM and 92 nM in HCT-116, HeLa, and A375 cells, respectively). Acts as a highly potent, reversible, ATP-competitive inhibitor of Cdk1/cyclin B and Cdk2/cyclin A (IC_{50} = 600 pM and 500 pM, respectively) with selectivity over VEGF-R2 (IC_{50} = 32 nM), GSK-3ß (IC_{50} = 140 nM), and a panel of eight other kinases (IC_{50} ≥ 1 µM).	1 mg

Glycogen Synthase Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cdk1/5 Inhibitor	**217720**	**(3-Amino-1H-pyrazolo[3,4-b]quinoxaline)** A 3-amino substituted pyrazoloquinoxaline compound that acts as a selective inhibitor of cyclin-dependent kinases 1 and 5 (Cdks; IC_{50} = 0.6 µM and 0.4 µM for Cdk1/cyclin B and Cdk5/p25, respectively). Also shown to inhibit GSK-3ß with (IC_{50} = 1 µM). Does not inhibit Cdc25 phosphatase activity (IC_{50} > 10 µM).	5 mg
GSK-3 Inhibitor IX	**361550**	**[BIO; (2'*Z*,3'*E*)-6-Bromoindirubin-3'-oxime]** A cell-permeable bis-indolo (indirubin) compound that acts as a highly potent, selective, reversible, and ATP-competitive inhibitor of GSK-3α/ß (IC_{50} = 5 nM). Its specificity has been tested against various Cdk's (IC_{50} = 83, 300, 320, and 10,000 nM for Cdk5/p25, Cdk2/A, Cdk1/B, and Cdk4/D1, respectively) as well as many other commonly studied kinases (IC_{50} ≥ 10 µM), including MAP kinases, PKA, PKC isoforms, PKG, CK, and IRTK. Inhibition of GSK by BIO has been shown to result in the activation of Wnt-signaling pathway and sustained pluripotency in human and murine ESCs (embryonic stem cells). Reported to maintain self-renewal in human and mouse embryonic stem cells. Also induces the differentiation of neonatal cardiomyocytes. A 10 mM (500 µg/140 µl) solution of GSK-3 Inhibitor IX (Cat. No.361552) in DMSO is also available.	1 mg
InSolution™GSK-3 Inhibitor IX	**361552**	A 10 mM (500 µg/140 µl) solution of GSK-3 Inhibitor IX (Cat. No. 361550) in DMSO.	500 µg
GSK-3 Inhibitor X	**361551**	**[BIO-Acetoxime; (2'*Z*,3'*E*)-6-Bromoindirubin-3'-acetoxime]** An acetoxime analog of BIO, GSK-3 Inhibitor IX (Cat. No.361550) that exhibits greater selectivity for GSK-3α/ß (IC_{50} = 10 nM) over Cdk5/p25, Cdk2/A and Cdk1/B (IC_{50} = 2.4 µM, 4.3 µM and 63 µM, respectively). Weakly affects the activities of Cdk4/D1 and many other kinases (IC_{50} ≥ 10 µM). Also acts as an aryl hydrocarbon receptor agonist in both yeast (EC_{50} ≥ 0.1 µM) and mammalian (EC_{50} = 0.16 µM) reporter systems.	1 mg
GSK-3 Inhibitor XIII	**361555**	**[(5-Methyl-1H-pyrazol-3-yl)-(2-phenylquinazolin-4-yl)amine]** An aminopyrazole compound that acts as a potent and ATP-binding site inhibitor of GSK-3 with a K_i of 24 nM.	1 mg 5 mg
GSK-3 Inhibitor XIV, Control, MeBIO	**361556**	**(1-Methyl-BIO)** A cell-permeable N-methylated analog of GSK-3 Inhibitor IX, BIO (Cat. No.361550) that serves as a relevant kinase inactive control (IC_{50} > 92 µM for Cdk1/B, > 100 µM for Cdk5/p25, and GSK-3α/ß). Acts as a potent ligand for aryl hydrocarbon receptor (AhR; EC_{50} = 20 nM and 93 nM for yeast and hepatoma reporter systems, respectively) and displays antiproliferative properties.	1 mg
GSK-3 Inhibitor XV	**361558**	The racemic mixture of a cell-permeable pyridocarbazolo-cyclopentadienyl Ruthenium complex that acts as a reversible, ATP-competitive, and highly potent inhibitor of GSK-3 (IC_{50} = 0.4 and 0.6 nM for GSK-3α and GSK-3ß, respectively) with 15-fold selectivity over PIM-1 kinase (IC_{50} = 3 nM). Studies using isolated enantiomers have shown that the *(R)*-enantiomer is GSK-3-selective (IC_{50} = 0.35, 0.55, and 35 nM for GSK-3α GSK-3ß, and Pim-1, respectively) and interferes with normal zebrafish embryo development (1 µM), while the *(S)*-enantiomer is Pim-1-selective (IC_{50} = 80, 90, and 3 nM for GSK-3α GSK-3ß, and Pim-1, respectively) and exhibits no effect in embryo development at the same dosage.	1 mg
GSK-3 Inhibitor XVI	**361559**	**6-(2-(4-(2,4-Dichlorophenyl)-5-(4-methyl-1H-imidazol-2-yl)-pyrimidin-2-ylamino)ethyl-amino)-nicotinonitrile** A cell-permeable aminopyrimidine compound that acts as potent, ATP-competitive, and highly selective GSK-3 inhibitor (IC_{50} = 10 and 6.7 nM against GSK-3α and GSK-3ß, respectively). Exhibits little or no activity toward 46 other enzymes (IC_{50} >8.8 µM against 20 kinases and K_i ≥5 µM against 23 non-kinase enzymes) and shows only weak binding to 22 pharmacologically relevant receptors (K_d ~4 µM). This compound is orally available and is shown to effectively improve glucose metabolism in both murine and rat type 2 diabetes models *in vivo*.	5 mg
GSK-3ß Inhibitor I	**361540**	**(TDZD-8; 4-Benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione)** A thiadiazolidinone (TDZD) analog that acts as a highly selective, non-ATP competitive inhibitor of GSK-3ß (IC_{50} = 2 µM). Inhibits Flt-3 and PKC activities (IC_{50} = 673 nM and 1.4-5.5 µM, respectively). Does not significantly affect the activities of Cdk-1/cyclin B, CK-II, and PKA, (IC_{50} > 100 µM). Binds to the active site of GSK-3ß.	5 mg
GSK-3ß Inhibitor II	**361541**	**{Glycogen Synthase Kinase-3ß Inhibitor II; 2-Thio(3-iodobenzyl)-5-(1-pyridyl)- [1,3,4]-oxadiazole}** A 2-thio-[1,3,4]-oxadiazole-pyridyl derivative that acts as a potent inhibitor of glycogen synthase kinase-3ß (IC_{50} = 390 nM).	5 mg
GSK-3ß Inhibitor VI	**361547**	**[2-Chloro-1-(4,5-dibromo-thiophen-2-yl)-ethanone]** A thienyl α-chloromethyl ketone compound that acts as a cell-permeable, irreversible, and non-ATP competitive inhibitor of GSK-3ß (IC_{50} = 1 µM). This reactive alkylating agent is selective towards GSK-3ß and does not affect PKA activity even at concentrations as high as 100 µM.	5 mg

Glycogen Synthase Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
GSK-3ß Inhibitor VII	**361548**	**(α-4-Dibromoacetophenone; Tau Protein Kinase I Inhibitor; TPK I Inhibitor)** A phenyl α-bromomethyl ketone compound that acts as a cell-permeable, and non-ATP competitive inhibitor of GSK-3ß (IC_{50} = 0.5 µM). This reactive alkylating agent is selective towards GSK-3ß and does not affect PKA activity even at concentrations as high as 100 µM.	5 mg
GSK-3ß Inhibitor VIII	**361549**	**[AR-A014418; N-(4-Methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-yl)urea]** A cell-permeable thiazole-containing urea compound that acts as a potent inhibitor of GSK-3. Shown to inhibit GSK-3ß with high potency (IC_{50} = 104 nM). Inhibition is competitive with respect to ATP (K_i = 38 nM). Specificity has been reported using a panel of 28 different kinases, including Cdk2 and Cdk5 (IC_{50} > 100 µM). Shown to prevent tau phosphorylation at a GSK-3-specific site. Also shown to protect neuronal cells against Aß-mediated neurodegeneration *in vitro* and reduce tauopathy in mice *in vivo* (30 µmol/kg delivered with 40% PEG400 and 40% dimethylacetamide in water). Caution: Do not use delivering vehicles containing dimethylamine for *in vivo* studies, as it is highly toxic to animals. A 25 mM (5 mg/649 µl) solution of GSK-3ß Inhibitor VIII (Cat. No.361557) in DMSO is also available.	5 mg
InSolution™GSK-3ß Inhibitor VIII	**361557**	A 25 mM (5 mg/649 µl) solution of GSK-3ß Inhibitor VIII (Cat. No. 361549) in DMSO.	5 mg
GSK-3ß Inhibitor XI	**361553**	**{3-(1-(3-Hydroxypropyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-4-pyrazin-2-yl-pyrrole-2, 5-dione}** A cell-permeable azaindolylmaleimide compound that acts as a potent, specific, and ATP-competitive inhibitor of GSK-3ß (K_i = 25 nM) and minimally inhibits a panel of 79 commonly studied protein kinases, including several PKC isozymes. Shown to increase intracellular glycogen synthase activity in HEK293 cells with an EC_{50} of 32 nM and demonstrate metabolic stability in human liver microsomes (HLM; $t_{1/2}$ > 100 min).	1 mg
GSK-3ß Inhibitor XII, TWS119	**361554**	**(Neurogenesis Inducer, TWS119)** A cell-permeable pyrrolopyrimidine compound that acts as a potent inhibitor of GSK-3ß (IC_{50} = 30 nM). Binds to GSK-3ß with high-affinity (K_d = 126 nM) and increases the level of ß-catenin, a downstream substrate of GSK-3ß in the Wnt signaling pathway. Shown to selectively induce neuronal differentiation in both pluripotent murine embryonal carcinoma cells (P19; 30-40% at 1 µM) and embryonic stem cells (D3; 50-60% at 400 nM).	1 mg 5 mg
GSK-3ß Peptide Inhibitor	**361545**	**(H-KEAPPAPPQSpP-NH_2; L803)** A phosphorylated peptide that acts as a substrate-specific, competitive inhibitor of GSK-3ß (IC_{50} = 150 µM). At 200 µM, weakly inhibits the activities of Cdc2, Casein Kinase II, MAPK, PKA, PKB, and PKCδ.	1 mg
GSK-3ß Peptide Inhibitor, Cell-permeable	**361546**	**(L803-mts; Myr-N-GKEAPPAPPQSZP-NH_2)** A cell-permeable myristoylated form of GSK-3ß Peptide Inhibitor (Cat. No.361545) with a glycine spacer. Acts as a selective, substrate-specific, competitive inhibitor of GSK-3ß (IC_{50} = 40 µM). Does not affect the activities of Cdc2, PKB, and PKC. Shown to mimic insulin action, and activate glycogen synthase activity (~2.5-fold) in HEK293 cells and improve glucose tolerance in diabetic mice. Displays *in vivo* stability.	1 mg
ICG	**371957**	A cell-permeable alkaloid containing indole/maleimide/imidazole skeleton that acts as a potent, reversible and ATP-competitive inhibitor of Chk1 (IC_{50} = 100 nM) and GSK-3ß (IC_{50} = 500 nM). Inhibits G_2 DNA damage checkpoint-associated kinases, Chk2, Cdk1, and DNA-PK only at much higher concentrations (IC_{50} = 3 µM, 10 µM, and 10 µM, respectively). Only minimally affects the activities of a panel of 11 other kinases tested ($IC_{50} \geq$ 40 µM). When used in combination with γ-irradiation, it is also reported to selectively arrest the growth of MCF-7 cells lacking p53 function.	1 mg
Indirubin-3'-monoxime	**402085**	A potent, reversible, and ATP-compatible inhibitor of GSK-3ß (glycogen synthase kinase 3ß), Cdk1 (cyclin-dependent kinase1) and Cdk5 (IC_{50} = 22 nM, 180 nM, and 100 nM, respectively). Inhibits the proliferation of a large range of cells by arresting them in the G_2/M phase of the cell cycle. Inhibits Tau phosphorylation *in vitro* and *in vivo* at Alzheimer's disease-specific sites. Also reported to inhibit the *in vivo* phosphorylation of DARPP-32 by Cdk5 on Thr^{75}.	1 mg
Indirubin-3'-monoxime, 5-Iodo-	**402086**	A highly potent cell-permeable and reversible inhibitor of glycogen synthase kinase-3ß (GSK-3ß; IC_{50} = 9 nM). Also inhibits Cdk1 (IC_{50} = 25 nM) and Cdk5 (IC_{50} = 20 nM) activities. Acts by binding to the ATP-binding pocket of these enzymes.	1 mg
Indirubin-3'-monoxime-5-sulphonic Acid	**402088**	A potent, reversible, and selective inhibitor of Cdk1 (IC_{50} = 5 nM) and Cdk5 (IC_{50} = 7 nM) and glycogen synthase kinase-3ß (GSK-3ß; IC_{50} = 80 nM). The inhibition is competitive with respect to ATP.	1 mg
Kenpaullone	**422000**	**{9-Bromo-7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one; NSC-664704}** A potent, cell-permeable, and reversible inhibitor of glycogen synthase kinase-3ß (IC_{50} = 230 nM), Lck (IC_{50} = 470 nM), and cyclin-dependent kinases (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). Also inhibits other kinases such as c-Src (IC_{50} = 15 µM), casein kinase II (IC_{50} = 20 µM), ERK1 (IC_{50} = 20 µM), and ERK2 (IC_{50} = 9 µM). Inhibition is competitive with respect to ATP binding.	1 mg

Glycogen Synthase Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Ro-31-8220	**557520**	**{3-[1-[3-(Amidinothio)propyl-1H-indol-3-yl]-3-(1-methyl-1H-indol-3-yl)maleimide; Bisindolylmaleimide IX, Methanesulfonate}** A cell-permeable, reversible, competitive, and selective inhibitor of protein kinase C (PKC; IC_{50} = 10 nM) over CaM kinase II (IC_{50} = 17 µM) and protein kinase A (IC_{50} = 900 nM). Potently inhibits GSK-3 in primary adipocytes (IC_{50} = 6.8 nM) and in GSK-3ß immunoprecipitates (IC_{50} = 2.8 nM). An inhibitor of MAP kinase phosphatase-1 expression and an activator of JNK1. Inhibits the phosphorylation of Raf-1 and induces apoptosis, independent of its effects on PKC, in HL-60 cells. Also inhibits sirtuin in a NAD-competitive manner (IC_{50} = 3.5 µM and 0.8 µM for SIRT1 and SIRT2, respectively), and induces hyperacetylation of tubulin in A549 cells. A 5 mM (500 µg/181 µl) solution of Ro-31-8220 (Cat. No.557521) in H_2O is also available.	500 µg
UCN-01	**539644**	**(Staurosporine, 7ß-Hydroxy,** *Streptomyces* **sp; 7-Hydroxystaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derived anticancer agent that reversibly and ATP-competitively inhibits several protein kinases (IC_{50} = 29 nM, 34 nM, 30 nM, 590 nM and 530 nM for PKCα, PKCß, PKCγ, PKCδ and PKC; IC_{50} = 7 nM, 27 nM, 50 nM, 50 nM, 150 nM and 1.04 µM for Chk1, Cdc25C-associated protein kinase 1, Cdk1, PAK4, Cdk5/p25 and Chk2; IC_{50} = 33 nM, 50 nM, 95 nM, 500 nM, 500 nM and 1.0 µM for PDK1, lck, MAPKAP kinase-2, Akt, GSK-3ß and PKA, respectively). At higher concentrations (> 15 µM), affects the activities of Src, PIM-1, CKII, DNA-PK, ErK1, ILK-1 and MAPKK1). Reported to suppress thymidylate synthase expression, induce apoptosis with caspase activation, and sensitize tumor cells to a range of DNA-damaging agents.	500 µg

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Product Citations:

Angus J M Cameron, Cristina Escribano, Adrian T Saurin, Brenda Kostelecky & Peter J Parker. PKC maturation is promoted by nucleotide pocket occupation independently of intrinsic kinase activity. *Nature Structural & Molecular Biology* **16,** 624 - 630 (2009).

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Inhibitor Libraries

Product	Cat. No.	Comments	Size
InhibitorSelect™ 384-Well Protein Kinase Inhibitor Library I	**539743**	Consists of 160 well-characterized, cell-permeable, potent, and reversible protein kinase inhibitors; the majority of which are ATP-competitive. They are supplied in a convenient 384-well plate format at a concentration of 10 mM in DMSO. The inhibitors in this library will be useful for target identification in drug discovery, biochemical pathway analysis, high-throughput kinase profiling, and other pharmaceutical-related applications.	384-well
InhibitorSelect™ 96-Well Protein Kinase Inhibitor Library I	**539744**	Consists of 80, well-characterized, cell-permeable, potent and reversible protein kinase inhibitors; the majority of which are ATP-competitive. They are supplied in a convenient 96-well plate format at a concentration of 10 mM in DMSO. The inhibitors in this library will be useful for target identification in drug discovery, biochemical pathway analysis, screening new protein kinases, and other pharmaceutical-related applications.	96-well
InhibitorSelect™ 96-Well Protein Kinase Inhibitor Library II	**539745**	Consists of 80, well-characterized, cell permeable, potent and reversible protein kinase inhibitors; the majority of which are ATP-competitive. They are supplied in a convenient 96-well plate format at a concentration of 10 mM in DMSO. The inhibitors in this library will be useful for target identification in drug discovery, biochemical pathway analysis, screening new protein kinases, and other pharmaceutical-related applications.	96-well
InhibitorSelect™ 96-Well Protein Kinase Inhibitor Library III	**539746**	Consists of 84, well-characterized protein kinase inhibitors, the majority of which are cell-permeable and ATP-competitive. This serine/threonine-selective library will be useful for target identification in drug discovery, biochemical pathway analysis, screening new protein kinases, and other pharmaceutical-related applications.	96-well
StemSelect™ Regulators 384-Well I	**569744**	Over 300 pharmacologically active, cell-permeable, potent and reversible signaling pathway regulators. They are supplied in a convenient 384-well plate format at a concentration of 0.1-10 mM in DMSO or H_2O (25 µl volume). The reagents in this library are useful as chemical probes to study the survival, migration, proliferation, and differentiation of cancer stem cells, stem cells fate, biochemical pathways, and other pharmacological applications.	1 ea

Interleukin Receptor Kinase Inhibitors

Product	Cat. No.	Comments	Size
Interleukin-1 Receptor-Associated-Kinase-1/4 Inhibitor	**407601**	**[IRAK-1/4 Inhibitor; N-(2-Morpholinylethyl)-2-(3-nitrobenzoylamido)-benzimidazole]** A cell-permeable benzimidazole compound that acts as a potent and selective inhibitor of interleukin-1 receptor-associated kinases (IC_{50} = 300 nM and 200 nM for IRAK-1 and -4). Shown to exhibit little activity against a panel of 27 other kinases (IC_{50} >10 µM), including lck and src.	5 mg

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 and cellular migration. It regulates the contractile interaction between actin microfilaments and conventional smooth muscle and non-muscle myosin II. There are three homologs of MLCK that share a similar catalytic domain. The smooth muscle (sm) MLCK is expressed ubiquitously, whereas skeletal muscle (sk) MLCK is expressed in skeletal muscle and cardiac (c) MLCK only in the cardiac tissue. The regulatory mechanisms of MLCK are also conserved in all MLCKs. 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. MLCK phosphorylates a specific site on the N-terminus of the regulatory light chain of myosin II. This phosphorylation is responsible for coupling increased Ca^{2+} concentration with smooth muscle contraction.

In the presence of Ca^{2+}, the C-terminal domain of calmodulin binds to the N-terminus of the calmodulin-binding sequence of MLCK followed by the binding of the N-terminal domain to the C-terminus of the calmodulin-binding sequence. 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**	**[N-(2-Aminoethyl)-5-chloronaphthalene-1-sulfonamide, HCl]** A cell-permeable, reversible, and shorter alkyl chain derivative of W-7 that inhibits casein kinase I (K_i = 80 µM), casein kinase II (K_i = 5.1 µM), myosin light chain kinase (K_i = 7.4 µM), protein kinase A (K_i = 4.3 µM), protein kinase C (K_i = 47 µM), and protein kinase G (K_i = 3.8 µM).	10 mg
Gö 7874, Hydrochloride	**365252**	A cell-permeable, potent, reversible, ATP-competitive, and selective inhibitor of protein kinase C (IC_{50} = 4 nM for rat brain PKC). Inhibits protein kinase A (IC_{50} = 510 nM), protein kinase G (IC_{50} = 4.8 µM), and myosin light chain kinase (IC_{50} = 120 nM) at much higher concentrations.	500 µg
InSolution™K-252a, *Nocardiopsis* sp.	**420297**	A 1 mM (100 µg/214 µl) solution of K-252a (Cat. No. 420298) in anhydrous DMSO.	100 µg
K-252a, *Nocardiopsis* sp.	**420298**	A cell-permeable, reversible, and ATP-competitive inhibitor against multiple protein kinases, including, but not limited to, CaM kinase II (K_i = 1.8 nM), myosin light chain kinase (K_i = 20 nM), protein kinase A (K_i = 18 nM), protein kinase C (K_i = 25 nM), protein kinase G (K_i = 20 nM), NGF receptor $gp140^{trk}$ (IC_{50} = 3 nM), its transforming *trk* oncogenes, and the related neurotrophin receptors $gp145^{trkB}$ and $gp145^{trkC}$. Reported to induce apoptosis and cell cycle arrest by decreasing Cdk1 and Cdc25c activity in T98G cells and inhibit Flt3 phosphorylation in Flt3/Itd-BaF3 cells (IC_{50} <50 nM). Also available as a premade 1 mM (100 µg/214 µl) solution in DMSO (Cat. No.420297).	100 µg
K-252b, *Nocardiopsis* sp.	**420319**	A cell-permeable, reversible, ATP-competitive, and non-selective inhibitor of protein kinase C (K_i = 20 nM), myosin light chain kinase (K_i = 147 nM), protein kinase A (K_i = 90 nM), and protein kinase G (K_i = 100 nM).	50 µg 100 µg
ML-7, Hydrochloride	**475880**	**[1-(5-Iodonaphthalene-1-sulfonyl)homopiperazine, HCl]** A cell-permeable, potent, reversible, ATP-competitive, and selective inhibitor of myosin light chain kinase (K_i = 300 nM). Inhibits protein kinase A (K_i = 21 µM) and protein kinase C (K_i = 42 µM) at much higher concentrations.	1 mg
ML-9, Hydrochloride	**475882**	**[1-(5-Chloronaphthalene-1-sulfonyl)homopiperazine, HCl]** A cell-permeable, reverisible and ATP-competitive inhibitor of myosin light chain kinase (K_i = 3.8 µM), protein kinase A (K_i = 32 µM), and protein kinase C (K_i = 54 µM). Also inhibits catecholamine secretion in intact and permeabilized chromaffin cells.	1 mg
Myosin Light Chain Kinase Inhibitor Peptide 18	**475981**	**(H-RKKYKYRRK-NH_2; MLCK Inhibitor Peptide 18)** A highly basic, cell-permeable, nonapeptide that acts as a selective Myosin Light Chain Kinase (MLCK) inhibitor (IC_{50} = 50 nM). The inhibition is competitive with respect to the peptide substrate (K_i = 52 nM) and displays a mixed mode of inhibition with respect to ATP. Does not interfere with kinase activation by calmodulin (CaM), nor does it inhibit the activities of CaMKII and PKA.	5 mg
Piceatannol	**527948**	**(*trans*-3,3',4,5'-Tetrahydroxystilbene)** A cell-permeable, substrate competitive and reversible plant metabolite that inhibits the activity of rat liver protein kinase A catalytic subunit (IC_{50} = 3 µM), PKC (IC_{50} = 8 µM), MLCK (IC_{50} = 12 µM). In RBL-2H3 cells, the selective inhibition of Syk by piceatannol results in inhibition of FceR1-mediated signaling. Also inhibits wheat embryo Ca^{2+}-dependent protein kinase (CDPK) (IC_{50} = 19 µM), and $p72^{syk}$ (IC_{50} = 10 µM), a non-receptor tyrosine kinase, relative to Lyn in isolated enzyme preparations. Also possesses anti-leukemic properties. Reported to activate sirtuins and promote the survival of eukaryotic cells.	1 mg
Staurosporine, *Streptomyces* sp.	**569397**	A potent, cell-permeable, reversible, ATP-competitive and broad spectrum inhibitor of protein kinases. Inhibits protein kinase A (IC_{50} = 7 nM), CaM kinase (IC_{50} = 20 nM), myosin light chain kinase (IC_{50} = 1.3 nM), protein kinase C (IC_{50} = 700 pM), and protein kinase G (IC_{50} = 8.5 nM). Also inhibits platelet aggregation induced by collagen or ADP but has no effect on thrombin-induced platelet aggregation. Induces apoptosis in human malignant glioma cell lines. Arrests normal cells at the G_1 checkpoint. A 1 mM (100 µg/214 µl) solution of Staurosporine (Cat. No.569396) in DMSO is also available.	100 µg 250 µg
W-12, Hydrochloride	**681635**	**[N-(4-Aminobutyl)-2-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 300 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 260 µM).	1 mg
W-13, Hydrochloride	**681636**	**[N-(4-Aminobutyl)-5-chloro-2-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 58 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 68 µM).	1 mg
W-5, Hydrochloride	**681625**	**[N-(6-Aminohexyl)-1-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 230 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 240 µM).	1 mg
W-7, Hydrochloride	**681629**	**[N-(6-Aminohexyl)-5-chloro-1-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 51 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 28 µM).	10 mg

p21 Activated Kinase Inhibitors

Product	Cat. No.	Comments	Size
p21-Activated Kinase Inhibitor III, IPA-3	**506106**	**(IPA-3; PAK Inhibitor III; 2,2'-Dihydroxy-1,1'-dinaphthyldisulfide)** A cell-permeable symmetrical disulfide allosteric inhibitor that selectively targets the autoregulatory domain of group I, but not group II, PAKs (p21-activated kinases) and prevents the activation of PAK1/2/3 (% inhibition= 95, 70, and 60, respectively, with 10 µM inhibitor; IC_{50} = 2.5 µM for PAK1). Specificity test shows ≥ 50% inhibition, in the presence of 10 µM ATP and inhibitor, against 9 of 214 non-PAK human kinases. Shown to effectively suppress both basal and PDGF-induced PAK activation at 30 µM in mouse embryonic fibroblasts. IPA-3 does not inhibit the enzymatic activity of preactivated PAKs and reduction of the intramolecular disulfide bond of IPA-3 by DTT renders it inactive.	5 mg 25 mg
p21-Activated Kinase Inhibitor, Negative Control	**506102**	**[PAK18-R192A; H_2N-RKKRRQRRR~G~PPVIAPAPEHTKSVYTRS-CO_2H]** The inhibitory activity of p21-Activated Kinase Inhibitor PAK18 (Cat. No.506101) is rendered inactive with a single amino acid mutation (R192A). Serves as an inactive control peptide.	2 mg
p21-Activated Kinase Inhibitor, PAK18	**506101**	**[PAK Inhibitor, PAK18; H_2N-RKKRRQRRR~G~PPVIAPRPEHTKSVYTRS-CO_2H]** A PAK (p21-activated kinase) inhibitor peptide that is composed of the cell permeant TAT peptide sequence and an 18-mer Pro-rich PIX-interacting motif of PAK that disrupts PIX-PAK interaction, reduces cellular PAK phosphorylation, and induces neurodegenerative morphology in hippocampal neurons *in vitro*. Intracerebroventricular administration of PAK18 in mice resulted in Alzheimer-like disease phenotype *in vivo*. PIX-interacting motif sequence has also been shown to block ras-dependent tumor growth and PAK activation in NIH-3T3 cells. The inactive control peptide, PAK18-R192A, is also available (Cat. No.506102).	2 mg

p90 S6K Inhibitors

Product	Cat. No.	Comments	Size
RSK Inhibitor	**559285**	**[p90 Ribosomal S6 Kinase Inhibitor; SL0101; Kaempferol-3-O-(3",4"-di-O-acetyl-a-L-rhamnopyranoside)]** A cell-permeable Kaempferol (Cat. No.420345) glycoside that targets the the N-terminal kinase domain of p90 ribosomal S6 kinase and inhibits RSK kinase activity (IC_{50} = 89 nM with 10 µM ATP) in a selective, reversible, and ATP-competitive (K_i = 1 µM) manner. Shown to inhibit the proliferation of MCF-7, but not the normal breast cell line MCF-10A, and specifically block PDB-induced cellular phosphorylation of RSK substrate p140, but not that of RSK or RSK upstream kinases even at concentrations as high as 100 µM.	1 mg

PIM Kinase Inhibitors

Product	Cat. No.	Comments	Size
PIM1 Kinase Inhibitor II	**526520**	**[3-Cyano-4-phenyl-6-(3-bromo-6-hydroxy)phenyl-2(1H)-pyridone; 2-Hydroxy-3-cyano-4-phenyl-6-(3-bromo-6-hydroxyphenyl)pyridine]** A pyridone compound that acts as an ATP-competitive inhibitor of PIM1 kinase (IC_{50} = 50 nM) with excellent selectivity over PIM2 and MEK1/2 (IC_{50} > 20 µM).	5 mg
PIM-1 Inhibitor III	**526521**	The racemic mixture of a pyridocarbazolo-cyclopentadienyl Ruthenium complex that acts as a ATP-binding site-targeting, reversible, and highly potent inhibitor of PIM-1 (IC_{50} = 0.5 and 3 nM for the *(S)*- and *(R)*-enantiomer, respectively) with ~10-fold selectivity over GSK-3α (IC_{50} = 15 and 20 nM for the *(S)*- and *(R)*-enantiomer, respectively).	1 mg
PIM1 Kinase Inhibitor IV	**526522**	**[4-(3-(4-Chlorophenyl)-2,1-benzisoxazol-5-yl)-2-pyrimidinamine]** A pyrimidinyl-benzisoxazolo compound that interacts with Lys67 and Glu121 at the PIM1 active site and inhibits PIM1 kinase activity with a K_i value of 0.091 µM.	5 mg
PIM1/2 Kinase Inhibitor V	**526523**	**SMI-4a, (Z)-5-(3-Trifluoromethylbenzylidene)thiazolidine-2,4-dione** A cell-permeable thiazolidinedione compound that acts as a potent, ATP-competitive inhibitor against Pim-1/2 kinases (IC_{50} = 24 nM and 100 nM against Pim-1 and Pim-2, respectively), while exhibiting little or no activity against a panel of 58 other kinases (≤20% inhibition at 5 µM). One hour inhibitor treatment (0.5 µM) of HEK-293T cultures at the end of a 4 hour $^{32}PO_4$ incubation period results in nearly complete inhibition of the autophosphorylation of overexpressed Pim-1. Comparing to Inhibitor VI (Cat. No.526524), Inhibitor V is less reactive towards DYRK1α (20% vs. 68% inhibition with repsective inhibitor at 5 µM) and more potent in PC3 human prostate cancer cell killing (IC_{50} = 17 vs. 48 µM with repsective inhibitor).	5 mg
PIM1/2 Kinase Inhibitor VI	**526524**	**(Z)-5-(4-Propoxybenzylidene)thiazolidine-2,4-dione** A cell-permeable thiazolidinedione compound that acts as a potent, ATP-competitive inhibitor against Pim-1/2 kinases (IC_{50} = 150 nM and 20 nM against Pim-1 and Pim-2, respectively) as well as DYRK1α (68% inhibition of DYRK1α and Pim-2 at 5 µM), while exhibiting little or no activity against a panel of 57 other kinases (≤18% inhibition at 5 µM). Reported to exhibit antitumor activity both in PC3 human prostate cancer cultures *in vitro* (IC_{50} = 48 µM) and in JC adenocarcinoma-transplanted Balb/C mice *in vivo* (~46% tumor mass reduction on day 20; 50 mg/kg via daily i.p.).	5 mg

PIM Kinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Quercetagetin	**551590**	**(3,3',4',5,6,7-Hexahydroxyflavone)** A cell-permeable flavanol compound that acts a potent, ATP-competitive, and reversible inhibitor of PIM1 kinase (IC_{50} = 340 nM). Exhibits ≥7-fold selectivity over 8 other kinases tested, including PIM2 (IC_{50} = 3.45 µM), and little activity toward c-Abl even at concentrations as high as 200 µM. Inhibits cellular BAD phosphorylation (IC_{50} = 5.5 µM) and induces growth arrest (ED_{50} = 3.8 µM) in PIM1-expressing RWPE2 cells.	5 mg
UCN-01	**539644**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp; 7-Hydroxystaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derived anticancer agent that reversibly and ATP-competitively inhibits several protein kinases (IC_{50} = 29 nM, 34 nM, 30 nM, 590 nM and 530 nM for PKCα, PKCß, PKCγ, PKCδ and PKC; IC_{50} = 7 nM, 27 nM, 50 nM, 50 nM, 150 nM and 1.04 µM for Chk1, Cdc25C-associated protein kinase 1, Cdk1, PAK4, Cdk5/p25 and Chk2; IC_{50} = 33 nM, 50 nM, 95 nM, 500 nM, 500 nM and 1.0 µM for PDK1, lck, MAPKAP kinase-2, Akt, GSK-3ß and PKA, respectively). At higher concentrations (> 15 µM), affects the activities of Src, PIM-1, CKII, DNA-PK, ErK1, ILK-1 and MAPKK1). Reported to suppress thymidylate synthase expression, induce apoptosis with caspase activation, and sensitize tumor cells to a range of DNA-damaging agents.	500 µg

Polo-like Kinase Inhibitors

Product	Cat. No.	Comments	Size
Polo-like Kinase Inhibitor I	**528282**	**[Plk Inhibitor I; 5-(5,6-Dimethoxybenzimidazol-1-yl)-3-(4-methanesulfonyl-benzyloxy)-thiophene-2-carboxamide]** A thiophenecarboxamide compound that acts as a potent and ATP-binding site-targeting inhibitor of polo-like kinase 1 (IC_{50} = 126 nM) with excellent selectivity over IKK-2 and IKK-3 (IC_{50} > 16 µM).	5 mg
Polo-like Kinase Inhibitor II, BTO-1	**528283**	**[5-Cyano-7-nitro-2-(benzothiazolo-N-oxide)-carboxamide]** A cell-permeable **b**enzo**t**hiazolo-N-**o**xide compound that targets the ATP-binding pocket of polo-like kinase and is shown to inhibit Plk1 kinase activity in cell-free kinase assays (IC_{50} = 8.0 µM) and suppress the phosphorylation of cellular Plk1 substrate Cdc25C in rat kangaroo kidney-derived PTK cells (75% inhibition at 6.3 µM). BTO-1 treatment of cultured cells results in mitosis defects consistent with loss-of-Plk1 phenotypes seen in Plk1 RNAi-treated U20S cells, including the appearance of monopolar spindles and the reduction of γ-tubulin at the centrosomes. Plk1 inhibition by BTO-1 in HeLa cells results in a blockage of Rho and Rho-GEF recruitment, which is essential for the assembly of a functional contractile ring.	2 mg
Polo-like Kinase Inhibitor III	**528284**	**[Plk Inhibitor III; 5-(5,6-Dimethoxy-1H-benzimidazol-1-yl)-3-((2-(trifluoromethyl)-benzyl)oxy)thiophene-2-carboxamide]** A cell-permeable thiophene-benzimidazole compound that acts as a potent and reversible inhibitor against polo-like kinases (K_i against Plk1/2/3/4 = 4.8, 3.8, 8.0, and 163 nM , respectively), while exhibiting little or much reduced activity against 39 other commonly studied kinases. Preferentially inhibits the proliferation of a panel of 11 tumor cell lines (IC_{50} ≤0.7 µM) over normal human diploid fibroblasts (IC_{50} = 6.14 µM) in culture and is equally potent against the mdr-1-expressing MES-SA/DX5 and its parent non-drug resistant MES-SA uterine sarcoma cell line.	500 µg

Protein Kinase Inhibitor Set

Product	Cat. No.	Comments	Size
Protein Kinase Inhibitor Set	**476490**	Contains 500 µg of Ro-31-8220 (Cat. No.557520), 20 mg of Genistein (Cat. No.345834), 1 mg of KN-93, Water-Soluble (Cat. No.422711), 50 µg of KT5720 (Cat. No.420320), 100 µg of Staurosporine, *Streptomyces* sp. (Cat. No.569397), and 1 mg of U0126 (Cat. No.662005).	1 set

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Protein Tyrosine Kinase (PTK) Inhibitors

Phosphorylation of tyrosine residues modulate enzymatic activity and create binding sites for recruitment of downstream signaling proteins. Protein tyrosine kinases (PTKs) play a key role in the regulation of cell proliferation, differentiation, metabolism, migration, and survival. PTKs catalyze the transfer of γ-phosphoryl groups from ATP to tyrosine hydroxyls of proteins. 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: the tetrametric 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 are activated by a large number of stimuli including hormones, neurotransmitters, growth factors, and cytokines. 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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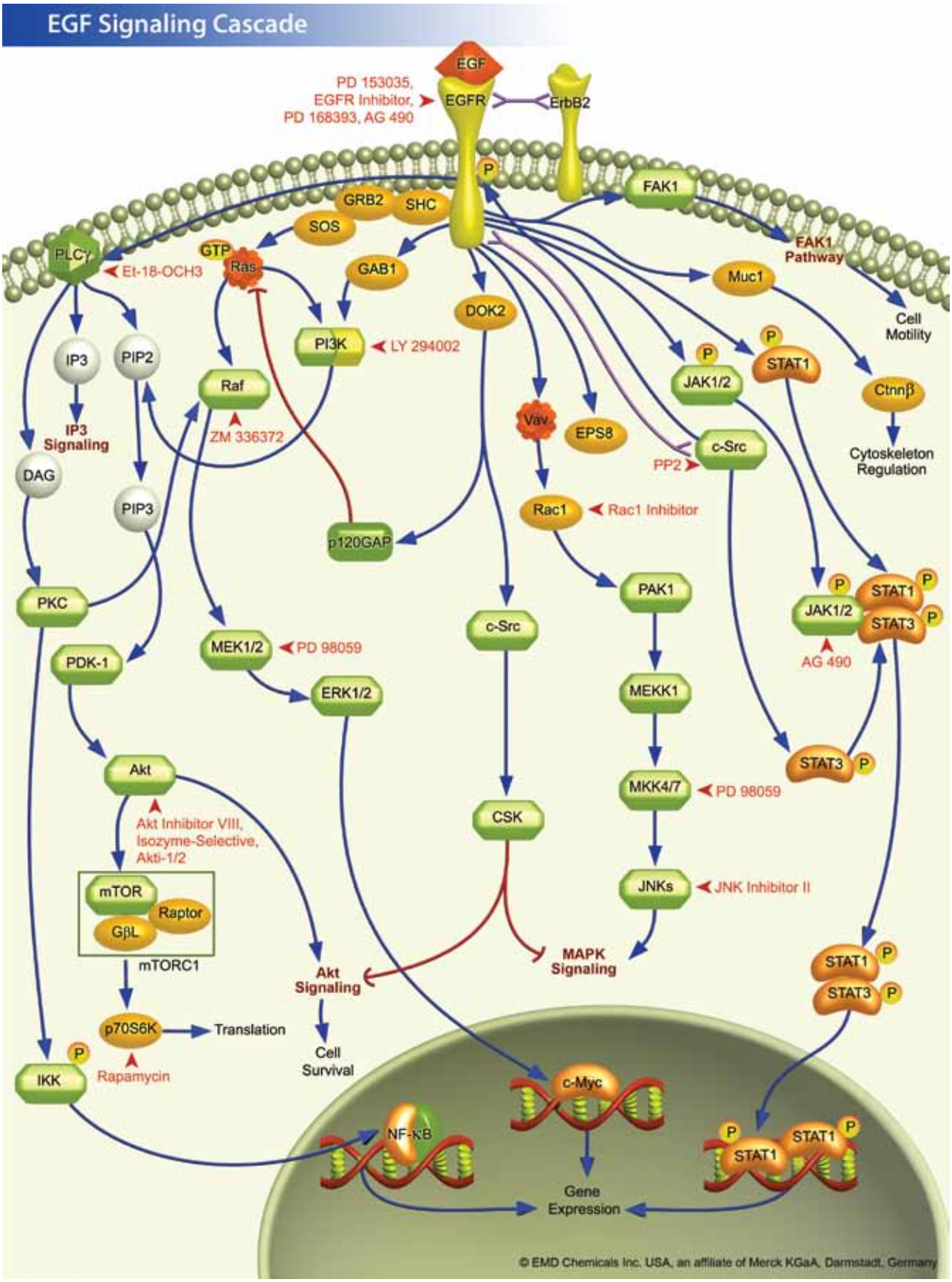
Highlighted below are inhibitors included in InhibitorSelect™ EGFR Signaling Pathway Inhibitor Panel (Cat. No. 324839). See page 71 or 204 for details.



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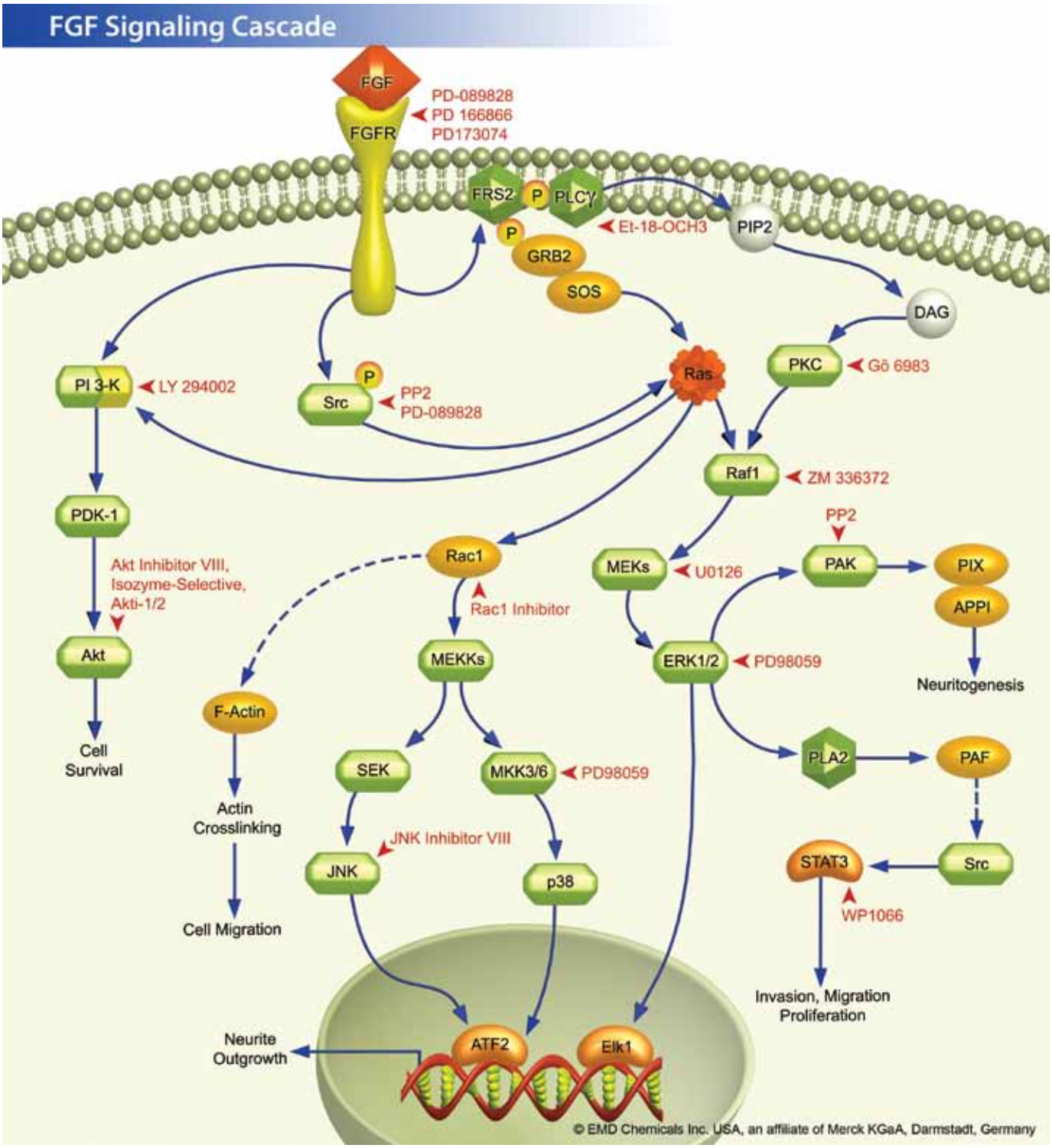
Highlighted below are inhibitors included in InhibitorSelect™ FGF Signaling Pathway Inhibitor Panel (Cat. No. 341612). See page 204 for details.



Protein Tyrosine Kinase (PTK) Inhibitors

Product	Cat. No.	Comments	Size
7BIO	**402087**	**[(2'Z,3'E)-7-Bromoindirubin-3'-oxime; 7-Bromoindirubin-oxime; Indirubin-3'-monoxime, 7-Bromo]** A cell-permeable 6-BIO (Cat. Nos.361550 and361552) structural isomer that acts as an ATP-competitive inhibitor of Flt3 (IC_{50} = 340 nM) and a caspase-independent, non-apoptotic cell death inducer (IC_{50} of cell survival ranges from 6.0 µM to 22.0 µM). Inhibition study against 75 other kinases reveals 10- to 80-fold selectivities over a group of 14 kinases, including TSF1, Aurora-A, and Aurora-B (IC_{50} = 3.3, 4.7, and 6.6 µM, respectively), up to 280-fold selectivities over a second group of 15 kinases, and little activity against the remaining 46 kinases of the panel (IC_{50} >100 µM).	5 mg
A77 1726	**100128**	**[N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxycrotoamide]** Leflunomide metabolite that blocks TNF-dependent NF-κB activation and gene expression. Inhibits the activity of dihydroorotate dehydrogenase (DHO-DH; IC_{50} = 220 nM). Reported to reduce IFN-γ-induced expression of iNOS in L929 fibroblasts. Inhibits IL-1ß-induced activation of COX-2 and PGE_2 synthesis (IC_{50} = 130 nM) in A549 cells. A cell-permeable, reversible, and substrate competitive inhibitor that inhibits the IL-2-induced tyrosine phosphorylation of JAK1 and JAK3.	5 mg
AG 1024	**121767**	**(3-Bromo-5-*t*-butyl-4-hydroxy-benzylidenemalonitrile)** A cell-permeable, reversible, substrate competitive, and specific inhibitor of insulin-like growth factor-1 (IGF-1) and insulin receptor tyrosine kinase activity. Exhibits lower IC_{50} values for IGF-1 than for the insulin receptor. Also inhibits insulin-stimulated cellular proliferation.	1 mg
AG 112	**658440**	**[2-Amino-4-(4'-hydroxyphenyl)-1,1,3-tricyanobuta-1,3-diene; Tyrphostin A48]** A cell-permeable, reversible, substrate competitive inhibitor of epidermal growth factor receptor tyrosine kinase (IC_{50} = 125 nM).	5 mg
AG 1295	**658550**	**(6,7-Dimethyl-2-phenylquinoxaline)** A cell-permeable, reversible, ATP-competitive, and selective inhibitor of platelet-derived growth factor (PDGF) receptor kinase (IC_{50} = 500 nM) and PDGF-dependent DNA synthesis (IC_{50} = 2.5 µM) in Swiss/3T3 cells. Has no effect on EGF receptor autophosphorylation and shows only a weak effect on EGF- or insulin-stimulated DNA synthesis. A potent blocker of smooth muscle cell proliferation.	5 mg
AG 1296	**658551**	**(6,7-Dimethoxy-3-phenylquinoxaline)** Similar to but more potent than AG 1295 (Cat. No.658550). A cell-permeable, reversible, and ATP-competitive, inhibitor of PDGF receptor kinase and blocks signaling of human PDGF α-receptors (IC_{50} = 1.0 µM) and ß-receptors (IC_{50} = 800 nM) as well as of the related stem cell factor receptor c-*kit* (80% inhibition at 5 µM). Affects neither the binding of PDGF-BB to the PDGF-ß receptor nor the receptor dimerization. Has no effect on autophosphorylation of the vascular endothelial growth factor receptor KDR or on DNA synthesis induced by vascular endothelial growth factor in porcine aortic endothelial cells. Also reverses the transformed phenotype of *sis*-transfected NIH/3T3 cells but has no effect on *src*-transformed NIH 3T3 cells or on the activity of the kinase $p60^{c\text{-}src}$ (F257) immunoprecipitated from these cells. Potently inhibits autophosphorylation in Flt3/Tel-BaF3 and Flt3/Itd-BaF3 cells with an IC_{50} of 300 nM and ~1 µM, respectively.	5 mg
AG 1387	**658520**	**[AG 555, 5-Iodo; α-Cyano-(3,4-dihydroxy)-5-iodo-N-(3-phenylpropyl)cinnamide; 2-Cyano-3-(3,4-dihydroxy-5-iodo-phenyl)-N-(3-phenylpropyl)acrylamide]** A reversible and substrate competitive 5-iodo analog of tyrphostin AG 555 (Cat. No.658404) that displays anticancer and antiviral properties. Reported to be more cell-permeable and potent than AG 555 as an inhibitor of protein tyrosine kinase and DNA topoisomerase I (TOPO I). In contrast to Camptothecin, *Camptotheca acuminata* (Cat. No.208925), AG 1387 inhibits the DNA relaxation activity of TOPO I by interacting with and preventing its binding to DNA. Also blocks and prevents murine AIDS (MAIDS) development by affecting both viral and/or cellular targets.	5 mg
AG 1433	**658553**	**[2-(3,4-Dihydroxyphenyl)-6,7-dimethylquinoxaline, HCl; SU 1433]** A potent, cell-permeable, reversible, and specific inhibitor of the PDGF-ß receptor kinase (IC_{50} = 5.0 µM) and of KDR/Flk-1/VEGF Receptor 2 (IC_{50} = 9.3 µM). Also acts as an angiogenesis inhibitor.	5 mg
InSolution™AG 1478	**658548**	Supplied as a 10 mM (1 mg/317 µl) solution of AG 1478 (Cat. No. 658552) in DMSO.	1 mg

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Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
AG 1478	**658552**	**[4-(3-Chloroanilino)-6,7-dimethoxyquinazoline]** A cell-permeable, reversible, ATP-competitive, highly potent and selective inhibitor of epidermal growth factor receptor kinase (IC_{50} = 3 nM) versus HER2-neu (IC_{50} >100 µM) and platelet-derived growth factor receptor kinase (IC_{50} >100 µM). Abolishes MAP kinase (ERK) activation induced by Angiotensin II (Cat. No.05-23-0101). Also inhibits the activation of EGFR kinase and MAP kinase by 4-hydroxynonenal. Downregulates ARF1 activity and disperses Golgi structure. A 10 mM (1 mg/317 µl) solution of AG 1478 (Cat. No.658548) in DMSO is also available.	5 mg
AG 17	**658425**	**[α-Cyano-(3,5-di-*t*-butyl-4-hydroxy)cinnamonitrile; 3,5-di-*t*-Butyl-4-hydroxy-benzylidenemalononitrile; NSC 242557; RG 50872; Tyrphostin A9]** Anti-proliferative agent that acts as a selective inhibitor of the platelet-derived growth factor receptor tyrosine kinase (IC_{50} = 500 nM). A potent, cell-permeable, reversible, and substrate competitive inhibitor of TNF-induced tyrosine phosphorylation of PYK2. Uncouples oxidative phosphorylation and induces apoptosis and cell growth arrest in NHL cell lines. Inhibits Cdk2 activity in lymphoma cell lines.	5 mg
AG 18	**658395**	**[α-Cyano-(3,4-dihydroxy)cinnamonitrile; RG-50810; Tyrphostin A23]** A broad-spectrum protein tyrosine kinase inhibitor. Inhibits epidermal growth factor receptor autophosphorylation (IC_{50} = 40 µM) and the GTPase activity of transducin (IC_{50} = 10 µM). Inhibits aldosterone secretion in response to Angiotensin II (Cat. No.05-23-0101). Suppresses the activation of MAP kinases by cholecystokinin in pancreatic acini.	5 mg
AG 213	**658405**	**[α-Cyano-(3,4-dihydroxy)thiocinnamide; RG-50864; Tyrphostin A47]** A cell-permeable, reversible, substrate competitive inhibitor of epidermal growth factor receptor tyrosine kinase activity (IC_{50} = 2.4 µM). Blocks HT-29 colon cancer cell proliferation and induces non-apoptotic cell death. Inhibits capacitative Ca^{2+} entry into cells.	5 mg
AG 30	**121760**	**[α-Cyano-(3,4-dihydroxy)cinnamic Acid; Tyrphostin AG 30]** A potent, cell-permeable, reversible, and substrate competitive protein tyrosine kinase (PTK) inhibitor specific for c-ErbB. Inhibits activation of STAT5 by c-ErbB in primary erythroblasts. Also causes induction of the differentiated phenotype in colon cancer cells which is associated with a marked decrease in PTK activity and tyrosine phosphorylation.	5 mg
AG 43	**658450**	**α-Cyano-(4-hydroxy)dihydrocinnamonitrile** Useful negative control for tyrphostins (IC_{50} = 6.5 mM) for epidermal growth factor receptor tyrosine kinase activity.	5 mg
AG 490	**658401**	**[α-Cyano-(3,4-dihydroxy)-N-benzylcinnamide; Tyrphostin B42]** A cell-permeable, reversible, substrate competitive, and potent inhibitor of epidermal growth factor receptor kinase autophosphorylation (IC_{50} = 100 nM). Inhibition of JAK2 by AG 490 selectively blocks leukemic cell growth *in vitro* and *in vivo* by inducing programmed cell death, with no harmful effect on normal hematopoiesis. Inhibits the constitutive activation of STAT-3 DNA binding and IL-2-induced growth of MF tumor cells. AG 490 has also been shown to inhibit the autokinase activity of JAK3. A 100 mM (5 mg/170 µl) solution of AG490 (Cat. No.658411) in DMSO is also available.	5 mg
AG 490, *m*-CF_3	**658408**	**[(α-Cyano-(3,4-dihydroxy)-N-(*m*-trifluoromethyl)benzylcinnamide]** A cell-permeable, reversible, substrate competitive, *m*-trifluoromethyl derivative of AG 490 (Cat. No. 658401) that displays apoptotic and antiproliferative properties (IC_{50} = 1.7 µM, 2.8 µM and 6.1 µM in 2E8, Baf/3 and Jurkat cells, respectively). Shown to inhibit IL-7-induced JAK3 tyrosine phosphorylation in 2E8 cells *in vitro* and significantly reduce lymph node cellularity in a murine B and T cell lymphoma model (1 mg per animal, i.p.) *in vivo*.	10 mg
AG 538	**658403**	**[α-Cyano-(3,4-dihydroxy)cinnamoyl-(3',4'-dihydroxyphenyl)ketone; Tyrphostin AG 538]** A potent, cell-premeable, reversible, and competitive inhibitor of IGF-1 receptor kinase (IC_{50} = 400 nM). Reaction is competitive with respect to IGF-1R substrate. Also inhibits the phosphorylation of PTK substrate poly(Glu,Tyr) by IGF-1R, IR, EGF-R, and Src (IC_{50} = 60 nM, 113 nM, 370 nM, and 2.4 µM, respectively). Inhibits the phosphorylation of PKB at a much higher concentration (IC_{50} = 76 µM).	5 mg
AG 556	**658415**	**α-Cyano-(3,4-dihydroxy)-N-(4-phenylbutyl)cinnamide** Selectively inhibits epidermal growth factor receptor kinase autophosphorylation (IC_{50} = 5 µM) over HER1/2 autophosphorylation. Also blocks LPS-induced TNF-α production and attentuates LPS-induced hypotension in rats.	5 mg
AG 82	**658400**	**[α-Cyano-(3,4,5-trihydroxy)cinnamonitrile; Tyrphostin A25]** A cell-permeable, reversible, and competitive inhibitor of substrate binding on protein tyrosine kinases. Inhibits epidermal growth factor receptor tyrosine kinase (IC_{50} = 3 µM) and the GTPase activity of transducin (IC_{50} = 7 µM). Inhibits neuromedin B-induced phosphorylation of $p125^{FAK}$ (focal adhesion kinase). Blocks the induction of inducible nitric oxide synthase in glial cells. Induces apoptosis in human leukemic cell lines.	5 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
AG 825	**121765**	**[4-Hydroxy-3-methoxy-5-(benzothiazolylthiomethyl)benzylidenecyanoacetamide]** A potent, cell-premeable, reversible, substrate competitive, and selective inhibitor of HER2 (*neu*/ErbB2; IC_{50} = 0.35 µM) relative to HER1 (IC_{50} = 19 µM) autophosphorylation. The inhibition is competitive with respect to ATP binding. Enhances chemosensitivity in non-small cell lung cancer (NSCLC) cell lines expressing high levels of $p185^{neu}$.	2 mg
AG 879	**658460**	**[α-Cyano-(3,5-di-*t*-butyl-4-hydroxy)thiocinnamide]** A cell-permeable, reversible, and substrate competitive inhibitor of nerve growth factor (NGF)-dependent $p140^{c\text{-}trk}$ tyrosine phosphorylation (EC_{50} = 10 µM) as well as NGF-induced phospholipase C-γ1 phosphorylation. Also blocks NGF-induced neurite outgrowth in PC12 cells. Does not affect the tyrosine phosphorylation of epidermal growth factor receptor or platelet-derived growth factor receptor. Inhibits insulin secretion in a dose-dependent manner.	5 mg
AG 9	**658390**	**{[(4-Methoxybenzylidene)malononitrile; α-Cyano-(4-methoxy)cinnamonitrile]; Tyrphostin A1}** An inactive compound that can be used as a negative control for inhibition of EGFR (IC_{50} >1250 µM for EGFR kinase). Has been shown to inhibit IL-2 stimulated Tyk-2 phosphorylation in ConA-activated T cells.	5 mg
InSolution™ AG490	**658411**	A 100 mM (5 mg/170 µl) solution of AG490 (Cat. No. 658401) in DMSO.	5 mg
AGL 2043	**121790**	**{1,2-Dimethyl-6-(2-thienyl)-imidazolo[5,4-g]quinoxaline; Tyrphostin AGL 2043}** A cell-permeable tricyclic quinoxaline compound that acts as a 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 PDGFß-receptor), Flt3, and Kit (IC_{50} = 1-3 µM). A weak inhibitor of PKA, EGFR, IGF-1R, VEGFR, and Src kinases (IC_{50} > 30 µM). Shown to be non-toxic. Potently inhibits smooth muscle cell proliferation and balloon-induced stenosis in pig heart. Displays enhanced aqueous solubility compared with its parent compound AG 1295 (Cat. No.658550).	1 mg
AGL 2263	**121850**	**(AG 2263)** A cell-permeable benzoxazolone-containing bioisostere of tyrphostin AG 538 (Cat. No.658403) that acts as a potent, substrate-competitive, but not ATP-competitive, inhibitor of insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF-1R). It is selective towards IR and IGF-1R (IC_{50} = 0.4 and 0.43 µM, respectively) and inhibits Src and PKB only at much higher concentrations (IC_{50} = 2.2 and 55 µM, respectively) in kinase assays. Shown to prevent IGF-1-induced cellular IGF-1R autophosphorylation and down stream signalling. Specifically inhibits IGF-1-induced, but not PDGF-induced, activation of PKB in cells. Effectively blocks the formation of colonies in soft agar by breast and prostate cancer cells. Exhibits improved cellular oxidative stability than AG 538.	5 mg
Angiogenesis Inhibitor	**175580**	**[(*Z,E*)-3-(Imidazol-4-ylmethylene)indolin-2-one]** A cell-permeable indolinone compound that displays anti-angiogenesis properties (30% inhibition of control at 10 µM in an *in vitro* rat aortic ring model) with a potency that is comparable to that of SU5416 (Cat. No.676487; 22% inhibition of control at 10 µM). Acts as a moderate ATP-competitive inhibitor of hEGF-R tyrosine kinase activity (54% inhibition at 10 µM).	10 mg
Bcr-abl Inhibitor	**197221**	**GNF-2; (3-(6)-(4-Trifluoromethoxy-phenylamino)-pyrimidin-4-yl)-benzamide** A cell-permeable and reverisble pyrimidine compound that binds to the c-abl myristoyl binding pocket and acts as an allosteric, non-ATP-competitive inhibitor of cellular Bcr-abl activity and Bcr-abl-dependent cellular functions. Exhibits little inhibitory effect against a panel of 63 kinases even at concentration as high as 10 µM. Exhibits potent and selective antiproliferative activity toward Bcr-abl-expressing cells (IC_{50} = 138 nM, 194 nM, 268 nM and 273 nM in Ba/F3.p210, Ba/F3.$p^{185Y253H}$, SUP-B15 and Ba/F3.$p^{210E255V}$, and K562, respectively). Brij-35 is reported to mask the inhibitory effect of GNF-2 in cell-free c-abl and Bcr-abl kinase assays.	5 mg
Bcr-abl Inhibitor II	**197223**	**{5-[(4-fluorobenzoyl)amino]-2-[(4-fluorobenzyl)thio]-1,3,4-thiadiazole}** A cell-permeable thiadiazole compound that acts as an ATP binding site-targeting inhibitor of Abl and c-Src kinases (K_i = 44 and 354 nM, respectively). Effectively inhibits cellular Bcr-Abl Tyr^{245} phosphorylation and the clonogenic activity of Bcr-Abl-transformed 32D cells, regardless of their resistance to Imatinib/STI571.	5 mg
BPDQ	**203697**	**{4-[(3-Bromophenyl)amino]-6,7-diaminoquinazoline}** A cell-permeable, reversible, ATP-competitive, potent and specific inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR; IC_{50} = 120 pM).	1 mg
BPIQ-I	**203696**	**{8-[(3-Bromophenyl)amino]-3-methyl-3H-imidazo[4,5-g]-quinazoline}** A cell-permeable, reversible, ATP-competitive, potent and specific inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR; IC_{50} = 25 pM).	1 mg

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Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
BPIQ-II	**203704**	**{8-[(3-Bromophenyl)amino]-1H-imidazo[4,5-g]-quinazoline}** A cell-permeable, reversible, ATP-competitive, potent and specific inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR; IC_{50} = 8 pM). Blocks EGF-mediated mitogenesis in Swiss/3T3 cells (IC_{50} = 46 nM).	1 mg
Bruton's Tyrosine Kinase Inhibitor III	**203661**	**{1-(3-(4-Amino-3-(4-phenyloxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one; N-Acryloyl-(3-(4-Amino-3-(4-phenyloxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine}** A cell-permeable pyrrolopyridinyl-acryloyl compound that acts as a highly potent, selective, and irreversible inhibitor of BTK (IC_{50} = 720 pM), while affecting Lyn, Lck, and Itk activity only at much higher concentrations (IC_{50} = 14 nM, 97 nM, and 1.0 µM, respectively). Inhibits BTK-dependent PLC-γ1 phosphorylation and Ca^{2+} flux in human B cell line Ramos *in vitro* (IC_{50} = 14 nM and 40 nM, respectively) and is of excellent efficacy in a murine rheumatoid archritis model *in vivo* (>95% inhibition at 10 mg/kg/day, p.o.).	1 mg
Butein	**203987**	**(2',4',3,4-Tetrahydroxychalcone)** A cell-permeable, reversible, substrate competitive, plant polyphenol that acts as a specific protein tyrosine kinase inhibitor. Potently inhibits the tyrosine kinase activity of the EGF receptor (IC_{50} = 65 µM) and $p60^{c\text{-}src}$ (IC_{50} = 65 µM). The inhibition is competitive with respect to ATP and non-competitive with respect to the substrate. Butein is also a potent antioxidant and anti-inflammatory agent. Has been shown to inhibit glutathione reductase and rat liver glutathione-S-transferase (IC_{50} = 9 µM). Reported to activate sirtuins and promote the survival of eukaryotic cells.	5 mg
c-Met Kinase Inhibitor II	**448102**	**[PHA665752; (3Z)-5-((2,6-Dichlorobenzyl)sulfonyl)-3-((3,5-dimethyl-4-(((2R)-2-(pyrrodin-1-ylmethyl)pyrrolidin-1-yl)carbonyl)-1H-pyrrol-2-yl)methylene)-1,3-dihydro-2H-indol-2-one]** A cell-permeable pyrrolo-indolinone compound that acts as an ATP-competitive and highly potent inhibitor of c-Met tyrosine kinase activity (IC_{50}= 9 nM) with good selectivity in both cell-free kinase assays (7.5-, 22-, 155-, and ≥333-fold over Ron, Flk1, c-abl, and a panel of 12 other commonly studied kinases, respectively) and in receptor autophosphorylation in cells (20- and 60-fold over Ron and Flk1, respectively). Shown to suppress c-Met-mediated cellular functions *in vitro* and inhibit tumorigenicity in various murine tumor models *in vivo*.	2 mg
c-Myc Inhibitor	**475956**	**(*Z*,*E*)-5-(4-Ethylbenzylidine)-2-thioxothiazolidin-4-one** A cell-permeable thiazolidinone compound that specifically inhibits the c-Myc-Max interaction, thereby preventing the transactivation of c-Myc target gene expression. Shown to inhibit tumor cell growth in a c-Myc-dependent manner both *in vitro* and *in vivo* (64 µM using c-Myc transfected Rat1a fibroblasts).	10 mg
cFMS Receptor Inhibitor II	**344037**	**[CSF-1 Receptor Inhibitor II; 4-(3,4-Dimethylanilino)-7-(4-pyridyl)quinoline-3-carboxamide]** A cell-permeable anilinoquinoline compound that acts as a potent, active site-targeting inhibitor of MCSF receptor/cFMS (IC_{50} = 80 nM). Although equally potent as cFMS Receptor Inhibitor III (Cat. No.344038) in inhibiting the cFMS-dependent growth of M-NSF-60 cells (IC_{50} = 0.1 µM), this inhibitor is much more selective against cFMS-independent growth of NSO cells (IC_{50} >50 µM).	1 mg
cFMS Receptor Inhibitor III	**344038**	**[CSF-1 Receptor Inhibitor III; 4-(3,4-Dimethylanilino)-7-(4-(methylsulfonyl)phenyl)quinoline-3-carboxamide]** A cell-permeable anilinoquinoline compound that acts as a potent, active site-targeting inhibitor of MCSF receptor/cFMS (IC_{50} = 8 nM). It is 100-fold more potent in inhibiting the cFMS-dependent growth of M-NSF-60 cells than the cFMS-independent growth of NSO cells (IC_{50} = 0.1 and 10 µM, respectively).	1 mg
cFMS Receptor Inhibitor IV	**344039**	**[CSF-1 Receptor Inhibitor IV; 5-Cyano-N-(2,5-di(piperidin-1-yl)phenyl)furan-2-carboxamide]** A cell-permeable furan carboxamide compound that acts as a potent, reversible, and ATP-competitive cFMS/CSF-1R inhibitor that blocks cFMS autophosphorylation both in CSF-1/M-CSF-stimulated HEK-293 cells (IC_{50} = 76 nM) and in cell-free *in vitro* kinase assays (IC_{50} = 17 nM).	5 mg
cFMS Receptor Tyrosine Kinase Inhibitor	**344036**	A cell-permeable diaminopyrimidine compound that acts as a potent, selective, and ATP-competitive inhibitor of cFMS kinase activity (IC_{50} = 30 nM) with minimal inhibition towards a panel of 26 other kinases (IC_{50} >5 µM). Shown to selectively inhibit cFMS-mediated cellular functions *in vitro* as well as CSF-1-dependent tumor growth *in vivo*. A 10 mM (1 mg/273 µl) solution of cFMS Receptor Tyrosine Kinase Inhibitor (Cat. No.344041) in DMSO is also available.	1 mg
InSolution™cFMS Receptor Tyrosine Kinase Inhibitor	**344041**	A 10 mM (1 mg/273 µl) solution of cFMS Receptor Tyrosine Kinase Inhibitor (Cat. No. 344036) in DMSO.	1 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
CL-387,785	**233100**	**{N-[4-[(3-Bromophenyl)amino]-6-quinazolinyl]-2-butynamide; EKI-785}** A cell-permeable and irreversible inhibitor of EGF-receptor (EGFR) kinase activity *in vivo* (IC_{50} = 250-490 pM) as well as EGF-stimulated autophosphorylation of tyrosine residues in the EGFR *in vivo* (IC_{50} = 5 nM). Blocks EGF-mediated growth in A431 cells. Inhibits proliferation of EGFR or c-ErbB2 expressing cells (IC_{50} = 31-125 nM) by covalently binding to the EGFR.	1 mg
Compound 56	**234505**	**{4-[(3-Bromophenyl)amino]-6,7-diethoxyquinazoline}** A cell-permeable, reversible, ATP-competitive, highly potent and specific inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (IC_{50} = 6 pM).	500 µg
Cucurbitacin I, *Cucumis sativus* L.	**238590**	**(JSI-124)** A cell-permeable and irreversible bitter triterpenoid compound (NCI identifier: NSC 521777) that displays anti-proliferative and antitumor properties both *in vitro* and *in vivo*. Acts as a potent and highly selective inhibitor of Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway. It suppresses STAT3 tyrosine phosphorylation in v-Src-transformed NIH 3T3 cells and human lung adenocarcinoma A549 cells (IC_{50} = 500 nM), resulting in inhibition of STAT3 DNA-binding and STAT3-mediated gene transcription. Shown to inhibit the growth of STAT3-transformed tumors in nude mice. Does not affect oncogenic pathways mediated by Ras, Akt, Erk1/2, or JNK.	1 mg
Daidzein	**251600**	**(4',7-Dihydroxyisoflavone)** Inactive analog of Genistein (Cat. No.345834). Blocks the G_1 phase of the cell cycle in Swiss/3T3 cells by inhibiting casein kinase II activity. Inhibits the growth of MiaPaC-2 and PANC-1 cells (IC_{50}= 45 µM and 75 µM, respectively).	25 mg
Damnacanthal	**251650**	**(3-Hydroxy-1-methoxyanthraquinone-2-aldehyde)** A cell-permeable, potent, reversible, and selective inhibitor of $p56^{lck}$ tyrosine kinase. Inhibits $p56^{lck}$ autophosphorylation (IC_{50} = 17 nM) and phosphorylation of an exogenous peptide by $p56^{lck}$ (IC_{50} = 620 nM). Exhibits over 100-fold greater selectivity for $p56^{lck}$ over PKA and PKC, 40-fold greater selectivity for $p56^{lck}$ over EGF receptor kinase, c-ErbB2, insulin receptor kinase, and PDGF receptor kinase, and 7 - 20-fold greater selectivity for $p56^{lck}$ over $p60^{src}$ and $p59^{fyn}$. Inhibition of $p56^{lck}$ is not significantly affected by the presence of sulfhydryl reagents. Also known to have antimalarial properties and to reverse the phenotype of *ras*-transformed cells.	1 mg
Daphnetin	**268295**	**(7,8-Dihydroxy-2H-1-benzopyran-2-one; 7,8-Dihydroxycoumarin)** A cell-permeable, substrate competitive, and reversible coumarin analog that acts as an inhibitor of several protein kinases. Inhibits EGFR kinase (IC_{50} = 7.67 µM), PKA (IC_{50} = 9.33 µM), and PKC (IC_{50} = 25 µM), *in vitro*. The inhibition of EGFR kinase by daphnetin was competitive to ATP and non-competitive to the peptide substrate. Also acts as a potent antioxidant and anti-malarial agent.	10 mg
5'-Deoxy-5'-methylthioadenosine	**260585**	**(MeSAdo; MTA)** A cell-permeable, reversible, and ATP-competitive naturally-occurring co-product of polyamine biosynthesis that acts as an endogenous substrate of methylthioadenosine phosphorylase (MTAP). Potently inhibits the protein carboxymethyltransferase and induces apoptosis in leukemia U937 cells. Also inhibits FGF-2 receptor tyrosine kinase activity as well as the proliferation of human astrocytes and glioma cells.	50 mg
DMBI	**317200**	**{(Z)-3-[4-(Dimethylamino)benzylidenyl]indolin-2-one}** A cell-permeable, reversible, ATP-competitive, and potent inhibitor of the tyrosine kinase activities of the PDGF ß-receptor (ß-PDGFR; IC_{50} = 4 µM in PAC-1 cells) and FGFR1 (IC_{50} = 5 µM for inhibition of tyrosine phosphorylation of p90). Does not inhibit EGFR or c-Src tyrosine kinases, even at concentrations greater than 100 µM.	10 mg
EGF/FGF/PDGF Receptor Tyrosine Kinase Inhibitor	**324841**	**{PD-089828; 1-(2-Amino-6-(2,6-dichlorophenyl) pyrido[2,3-d]pyrimidin-7-yl)-3-tert-butyl urea}** A cell-permeable and reversible protein tyrosine kinase inhibitor that inhibits human FGFR-1, PDGFR-ß, c-Scr, and EGFR (IC_{50} = 0.15, 0.18, 1.76, and 5.47 µM, respectively), while exhibiting little activity against InsR, PKC, or CDK4/Cyclin D1 (IC_{50} >50 µM). The inhibition is shown to be ATP-competitive in the case of FGFR-1, PDGFR-ß, and EGFR, but noncompetitive in the case of c-Src.	2 mg
EGFR Inhibitor	**324674**	**[Cyclopropanecarboxylic acid-(3-(6-(3-trifluoromethyl-phenylamino)-pyrimidin-4-ylamino)-phenyl)-amide]** A cell-permeable 4,6-dianilinopyrimidine compound that acts as a potent, ATP-competitive, and highly selective inhibitor of EGFR and some EGFR mutants (IC_{50} = 21 nM, 63 nM, and 4 nM for EGFRwt, $EGFR^{L858R}$ and $EGFR^{L861Q}$, respectively) vs. erbB4/Her4 (IC_{50} = 7.64 µM) and a panel of 55 other kinases. Shown to completely block EGF-induced EGFR autophosphorylation in U-2OS cells at 10 µM.	1 mg

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Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
EGFR Inhibitor II, BIBX1382	**324832**	**{BIBX1382BS; N^8-(3-Chloro-4-fluorophenyl)-N^2-(1-methylpiperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, 2HCl}** A cell-permeable pyrimidopyrimidine compound that acts as a potent, reversible, ATP-competitive, and highly selective inhibitor of EGFR (ErbB-1, HER-1) both in cell-free enzymatic reactions (IC_{50} = 3 nM) and in culture (IC_{50} = 0.15, 1.82, and 3.2 µM in EGF-, HGF-, and FCS-dependent thymidine incorporation, respectively, in KB cells). It exhibits 1,000-fold greater selectivity over ErbB-2 (HER-2, neu; IC_{50} = 3.4 µM) and shows little activity towards IGF1R, ß-InsRK, HGFR, c-src, and VEGFR-2 even at concentrations as high as 10 µM. Its antitumor efficacy has also been demonstrated in a murine xenograft model *in vivo* (10 mg/kg, daily, p.o.).	5 mg
EGFR Inhibitor III	**324833**	**[N-(4-((3,4-Dichloro-6-fluorophenyl)amino)-quinazolin-6-yl)-2-chloroacetamide]** A cell-permeable quinazolinyl-chloroacetamide compound that selectively and irreversibly blocks EGFR autophosphorylation with no effect on the expression levels of EGFR, and suppresses leiomyoma and myometrical cell proliferation (IC_{50} = 0.7 µM and 1.1 µM, respectively). Shown to induce apoptosis and cell cycle arrest, and in combination with Genistein (Cat. No.345834) completely suppress leiomyoma cell proliferation.	5 mg
EGFR/ErbB-2 Inhibitor	**324673**	**[4557W; 4-(4-Benzyloxyanilino)-6,7-dimethoxyquinazoline]** A cell-permeable 4-anilino quinazoline compound that acts a potent, reversible, and ATP-competitive inhibitors of EGFR and c-erbB2 (IC_{50} = 20 nM and 79 nM, respectively), members of the type I growth factor receptor family that is involved in breast cancer development and progression. Shown to effectively inhibit the proliferation (IC_{50} = ~ 1.2-2.5 µM) of tumor cells overexpressing EGRF or c-erbB-2.	1 mg
EGFR/ErbB-2/ErbB-4 Inhibitor	**324840**	**{N-(4-((3-Chloro-4-fluorophenyl)amino)pyrido[3,4-d]pyrimidin-6-yl)2-butynamide}** A cell-permeable, ATP-binding site-targeting alkynamidopyrimidine compound that acts as a potent and irreversible inhibitor of erbB activities (IC_{50} = 0.3, 1.1, and 0.5 nM for erbB-1, erbB-2, and erbB-4, respectively). Inhibits EGF- and heregulin-induced erbB autophosphorylation in NIH3T3-erbB-1 and in MDA-MB-453 cells (IC_{50} = 2.5 and 24 nM, respectively).	1 mg
Emodin	**324694**	**(6-Methyl-1,3,8-trihydroxyanthraquinone)** A cell-permeable, reversible, substrate competitive and potent $p56^{lck}$ tyrosine kinase inhibitor (IC_{50} = 18.5 µM). Selectively blocks the growth of *v-ras* transformed human bronchial epithelial cells (IC_{50} = 15 µM). Also suppresses HER2/neu tyrosine kinase activity in HER2/neu overexpressing breast cancer cells.	50 mg
ErbB2 Inhibitor II	**324732**	**[4-(3-Phenoxyphenyl)-5-cyano-2H-1,2,3-triazole]** A cell-permeable triazole compound that targets the ATP-binding site of erbB2/HER2 and reduces the phosphorylation of erbB2 in MDA-MB-453 cells (IC_{50} = 6.6 µM), but not that of the overexpressed erbB1 in MDA-MB-468 cells even at concentrations as high as 100 µM. Shown to suppress MDA-MB-453 growth with an IC_{50} of 30.9 µM.	5 mg
Erbstatin Analog	**324930**	**(2,5-Dihydroxymethylcinnamate)** A cell-permeable, reversible, substrate competitive and stable analog of erbstatin that acts as a competitive inhibitor of epidermal growth factor receptor-associated tyrosine kinase (IC_{50} = 780 nM). Inhibits the activation of v-Abl tyrosine kinase more effectively than erbstatin. Antagonistic to most other protein kinases at their catalytic sites. Induces apoptosis in mouse thymocytes and inhibits the G_2/M transition of the cell cycle.	1 mg
FGF Receptor Tyrosine Kinase Inhibitor	**341608**	**{PD 166866; 1-(2-Amino-6-(3,5-dimethoxyphenyl) pyrido[2,3-d]pyrimidin-7-yl)-3-tert-butyl urea}** A cell-permeable pyridopyrimidinyl urea compound that acts a potent, ATP-competitive inhibitor of FGFR (IC_{50} = 60 nM using FGFR1) with excellent selectivity over PDGFRß, EGFR, insulin receptor, and c-Src (IC_{50} > 50 µM).	5 mg
FGF Receptor Tyrosine Kinase Inhibitor IV	**341609**	**[NP603; (Z)-3-(5-(6-(3,5-Dimethoxyphenyl)-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrol-3-yl)-propionic acid]** A cell-permeable SU6668 (PDGFR Tyrosine Kinase Inhibitor VI, Cat. No.521235) derivative that targets the ATP-binding pocket and inhibits the kinase activity of FGFR1, PDGFRß, and VEGFR2 (IC_{50} = 520, 780, and 930 nM, respectively), while exhibiting little activity against EGFR (IC_{50} >100 µM). Shown to exhibit anti-angiogenesis activity and suppress FGF-2-induced proliferation (IC_{50} = 18.2 µM) in HUVEC cultures in a dose-dependent manner.	5 mg
FGF/PDGF/VEGF RTK Inhibitor	**341610**	**4-Hydroxy-3-benzimidazol-2-ylhydroquinolin-2-one** A cell-permeable benzimidazolo-hydroquinolinone compound that acts as a potent, reversible, ATP-competitive inhibitor against PDGFRß, FGFR-1, and VEGFR-2 (IC_{50} = 20, 90, and 240 nM, respectively) and effectively suppresses VEGF-stimulated proliferation of HMVECs (EC_{50} = 420 nM).	5 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
FGF/VEGF Receptor Tyrosine Kinase Inhibitor, PD173074	**341607**	**{PD173074; 1-t-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(4-diethylaminobutylamino)-pyrido[2,3-d]pyrimidin-7-yl)urea}** A cell-permeable pyridopyrimidine compound that acts as a potent, ATP-competitive, and reversible inhibitor of FGF and VEGF receptors (IC_{50} = 21.5 nM for FGFR1). It inhibits PDGFR and c-Src only at much higher concentration (IC_{50} = 17.6 µM, 19.8 µM, respectively) and exhibits little effect against EGFR, InsR, MEK, and cPKC even at concentrations as high as 50 µM. Shown to inhibit the autophosphorylation of endogenous FGFR1 (IC_{50} 50 *in vitro*, and FGF- and VEGF-induced angiogenesis in mice *in vivo*.	2 mg
Flt-3 Inhibitor	**343020**	A cell-permeable thienylcarboxamide compound that acts as a potent, ATP-competitive, and highly selective Flt-3 inhibitor (IC_{50} = 42 nM) with little effect against a panel of 22 other kinases (IC_{50} ≥3 µM). Shown to exhibit antiproliferative properties against the human acute myelogenous leukemia cell line MV4-11 (IC_{50} = 340 nM) expressing constitutively active Flt-3.	5 mg
Flt-3 Inhibitor II	**343021**	**[Bis-(5-hydroxy-1H-indol-2-yl)methanone]** A cell-permeable symmetrical indolylmethanone kinase inhibitor that is more selective toward Flt3 over PDGFR either in cell-based receptor autophosphorylation (IC_{50} = 40 nM vs. 300 nM) or in cell-free kinase reactions (IC_{50} = 33 nM vs. 171 nM) and potently induces apoptosis in Flt3-expressing primary AML patient blasts. Affects Abl- or Kit-dependent cell growth only at much higher concentrations (IC_{50} = 4.2 and ≥0.5 µM, respectively), while exhibiting little effect against IL-3-mediated cellular signaling. The molecular mechanism of inhibition is presumably due to interaction at the enzyme's ATP-binding site.	1 mg
Flt3 Inhibitor III	**343022**	**[(5-Phenyl-thiazol-2-yl)-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-amine; 5-Phenyl-N-(4-(2-(1-pyrrolidinyl)ethoxy)phenyl)-2-thiazolamine]** A cell-permeable 5-phenyl-2-thiazolamine compound that acts as a potent, ATP binding site-targeting inhibitor of Flt3 (IC_{50} = 50 nM). It inhibits c-Kit, KDR, c-Abl, Cdk1, c-Src, and Tie-2 only at much higher concentrations (IC_{50} = 0.26, 0.91, 1.2, 2.1, 2.8, and 8.0 µM, respectively) and exhibits little activity against a panel of 12 other commonly studied kinases even at concentrations as high as 10 µM. Blocks FLT3-dependent cell proliferation in a dose-dependent manner (IC_{50} = 52, 240, and 760 nM in MV4:11-ITD, BaF3-ITD, and BaF3-D835/Y cells).	5 mg
Flt3 Inhibitor IV	**343023**	**[4-(4-Aminophenyl)-1H-indazol-3-ylamine]** A 3-aminoindazole compound that acts as a potent and ATP-competitive inhibitor of Flt3 (IC_{50} = 43 nM) with excellent selectivity over KDR/VEGFR-2 and c-Kit (IC_{50} = 4.79 µM and 7.36 µM, respectively).	5 mg
Geldanamycin, *Streptomyces hygroscopicus*	**345805**	A benzoquinoid antibiotic that inhibits $p60^{c\text{-}src}$ tyrosine kinase and c-*myc* gene expression in murine lymphoblastoma cells. Geldanamycin has antiproliferative and antitumor effects. Rapidly depletes $p185^{c\text{-}erbB2}$ protein tyrosine kinase in breast carcinoma cells. Binds to HSP90 and disrupts Raf1-HSP90 complex leading to destabilization of Raf1. Inhibits basal and hypoxia-induced expression of c-Jun (IC_{50} = 75 nM) and abolishes hypoxia-induced increase in c-Jun N-terminal kinase activity. Also known to selectively destabilize mutated p53 protein from a number of breast, leukemia, and prostate cell lines.	100 µg
Genistein	**345834**	**(4',5,7-Trihydroxyisoflavone)** A cell-permeable, reversible, substrate competitive inhibitor of protein tyrosine kinases, including autophosphorylation of epidermal growth factor receptor kinase (IC_{50} = 2.6 µM). The inhibition is competitive with respect to ATP and non-competitive with respect to the phosphate acceptor. Has only a trivial effect on the activity of PKA and PKC (IC_{50} > 350 µM). Inhibits tumor cell proliferation and induces tumor cell differentiation. Produces cell cycle arrest and apoptosis in Jurkat T-leukemia cells. However, it prevents anti-CD3 monoclonal antibody-induced thymic apoptosis. Also inhibits topoisomerase II activity *in vitro*.	20 mg 50 mg
Genistin	**345836**	**(Genistein, 7-O-ß-D-Glucopyranoside)** An isoflavone glycoside found in soy-based food products. This is an inactive analog of the PTK inhibitor Genistein (Cat. No.345834) and can be used as a negative control for Genistein. Reported to reduce bone loss in ovarectomized rats.	5 mg
GTP-14564	**371806**	**(3-Phenyl-1H-benzofuro[3,2-c]pyrazole; 1-Phenyl-3-H-8-oxa-2,3-diaza-cyclopenta[a]inden)** A cell-permeable, reversible, and ATP-competitive tricyclic benzofurano-indazolo compound that acts as a potent and specific inhibitor of class III receptor tyrosine kinases (IC_{50} = 0.3 µM for c-fms, c-kit, wt-FLT3 and ITD-FLT3; 1.0 µM for PDGFRß). Does not affect the activities of KDR, EGFR, HER2, Abl, Src, PKA, AKT, PKC, MEK, or ERK1/2 (IC_{50} ≥ 10 µM). Has been used successfully to differentiate between the signalling pathways activated by wt-FLT3 and ITD-FLT3 in Ba/F3 cells.	5 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Herbimycin A, *Streptomyces* sp.	**375670**	A potent and cell-permeable protein tyrosine kinase inhibitor. Inhibits $p60^{v\text{-}src}$ (IC_{50} = 12 µM) and PDGF-induced phospholipase D activation (IC_{50} = 8 µg/ml). Reported to inhibit c-Src related bone resorption (IC_{50} = 70 nM). Inhibits angiogenesis in chick chorioallantoic membrane. Also shown to inhibit anti-CD3 monoclonal antibody-induced apoptosis of thymocytes.	100 µg
HNMPA-(AM)3	**397100**	**(Hydroxy-2-naphthalenylmethylphosphonic Acid Trisacetoxymethyl Ester; Pro-drug II)** A cell-permeable analog of HNMPA that yields the parent compound upon cleavage by cytosolic esterases. Inhibits insulin receptor tyrosine kinase (IC_{50} = 100 µM) and insulin-stimulated glucose oxidation in isolated rat adipocytes (IC_{50} = 10 µM). Also reported to inhibit tyrosine autophosphorylation of the human insulin receptor (IC_{50} = 200 µM).	5 mg
I-OMe-AG 538	**658417**	**[α-Cyano-(3-methoxy,4-hydroxy,5-iodo)cinnamoyl-(3',4'-dihydroxyphenyl)ketone; Tyrphostin I-OMe-AG 538]** A cell-permeable and reversible analog of AG 538 (Cat. No.658403) that acts as a competitive inhibitor of IGF-1 receptor kinase in intact cells in a dose-dependent manner. Exhibits enhanced cell-permeability and more resistance towards oxidation. Reported to inhibit IGF-1R kinase autophosphorylation (IC_{50} = 3.4 µM) as well as the phosphorylation of the PTK substrate poly(Glu,Tyr) (IC_{50} = 2 µM). Also inhibits the activation of the downstream targets PKB and ERK2 with the same potency as AG 538.	5 mg
IGF-1R Inhibitor II	**407248**	**[N-(2-Methoxy-5-chlorophenyl)-N'-(2-methylquinolin-4-yl)-urea]** A cell-permeable phenylquinolinyl-urea compound that inhibits IGF-1R autophosphorylation (IC_{50} = 12 µM in inhibiting ligand-induced autophosphorylation in MCF-7 cells and *in vitro* (IC_{50} = 8 and 15 µM for MCF-7 and MCNeuA, respectively) and in mice *in vivo* (80% reduction, 100 mg/kg thrice a week, i.p.). The mechanism of inhibition probably involves indirect blocking of ATP binding.	10 mg
IGF-1R Inhibitor, PPP	**407247**	**(Insulin-like Growth Factor-1 Receptor Inhibitor; Picropodophyllin)** A cell-permeable cis-cyclolignan compound that acts as a substrate competitive, reversible, potent, and specific inhibitor of IGF-1R both *in vitro* (IC_{50} = 1 nM in cell-free kinase assay; ≤ 60 nM for cell viability and receptor autophosphorylation in melanoma cell lines) and *in vivo* (complete inhibition of IGF-1R-dependent tumor cell growth at 20 mg/kg/12 hr, i.p., in SCID mice) with minimum toxic effect (LD_{50} > 500 mg/kg). Exhibits little effect towards IR, FGFR, PDGFR and EGFR, and exerts no effects on microtubules and DNA topoisomerase II. Targets the phosphorylation of Y1136 in the activation loop and is the first inhibitor reported to discriminate between IGF-1R and IR.	1 mg
InhibitorSelect™ EGFR Signaling Pathway Inhibitor Panel	**324839**	A panel containing 13 potent and selective inhibitors useful for the study of EGFR signaling pathway. This panel contains the following inhibitors: 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akt-1/2 (Cat. No.124018); 1 mg of PD 153035 (Cat. No.234490); 1 mg of EGFR Inhibitor (Cat. No.324674); 5 mg of Et-18-OCH_3 (Cat. No.341207); 5 mg of JNK Inhibitor II (Cat. No.420119); 5 mg of LY 294002 (Cat. N0.440202); 5 mg of PD 98059 (Cat. No.513000); 1 mg of PD 168393 (Cat. No.513033); 1 mg of PP2 (Cat. No.529573); 100 µg of Rapamycin (Cat. No.553210); 1 mg of SB 203580 (Cat. No.559389); 5 mg of AG 490 (Cat. No.658401) and 1 mg of ZM 336372 (Cat. No.692000). Also provided is 15 ml of anhydrous DMSO. Supplied with a data sheet.	1 ea
InSolution™JAK Inhibitor I	**420097**	**{2-(1,1-Dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz[h]-imidaz[4,5-f]isoquinolin-7-one}** A 10 mM (500 µg/162 µl) solution of JAK Inhibitor I (Cat. No. 420099) in DMSO.	500 µg
JAK Inhibitor I	**420099**	**{2-(1,1-Dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz[h]-imidaz[4,5-f]isoquinolin-7-one}** A potent, reversible, cell-permeable, and ATP-competitive 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). Inhibits other kinases at much higher concentrations. Shown to inhibit IL2- and IL4-dependent proliferation of CTLL cells and block the phosphorylation of STAT5; and further induce growth inhibition of multiple myeloma cells expressing activated JAKs and STAT3, unlike AG 490 (Cat. No.658401). A 10 mM (500 µg/162 µl) solution of JAK Inhibitor I (Cat. No.420097) in DMSO is also available.	500 µg
JAK2 Inhibitor II	**420132**	**(1,2,3,4,5,6-Hexabromocyclohexane)** A cell-permeable hexabromocyclohexane compound that interacts with a solvent-accessible pocket near the activation loop of JAK2 and acts as a specific, reverisble, and direct inhibitor of JAK2 autophosphorylation (maximal inhibition at 50 µM in BSC-40 cells overexpressing JAK2). Reduces growth hormone-mediated JAK2 activation in γ2A cells that stably express growth hormone receptor and JAK2. Does not block EGFR autophosphorylation in murine fibroblasts.	25 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
JAK2 Inhibitor III	**573098**	**[SD-1029; NSC 371488; 9-(3,4-Dichlorophenyl)-2,7-bis(dimethylaminomethyl)-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione, 2HBr]** A cell-permeable xanthenedione compound that acts as a JAK2-selective inhibitor. It exhibits much less effect on the cellular phosphorylation levels of Jak1 and Src and shows no significant inhibition towards a panel of 49 other protein kinases in cell-free kinase assays at a concentration of 10 µM. Effectively inhibits cell proliferation in JAK-activated BA/F3 cell lines as well as phosphorylation and nuclear translocation of cellular Stat3.	10 mg
JAK2 Inhibitor IV	**420139**	**[3-Amino-5-(N-tert-butylsulfonamido-4-phenyl)-indazole]** An aminoindazole compound that potently inhibits the activity of both the wild-type JAK2 and the constitutively active V617F mutant (IC_{50} = 78 and 206 nM, respectively) frequently found in patients with clonal polycythemia vera, essential thrombocytosis, and chronic idiopathic myelofibrosis, while exhibiting much reduced activity against JAK3 (IC_{50} = 2.93 µM).	5 mg
JAK3 Inhibitor I	**420101**	**[4-(4′-Hydroxyphenyl)amino-6,7-dimethoxyquinazoline; WHI-P131]** A cell-permeable, reversible, potent, ATP-competitive, and specific inhibitor of JAK3 (Janus family kinase 3; IC_{50} = 78 µM). Has no effect on JAK1, JAK2, or Zap/Syk or Src tyrosine kinases. Acts as a potent inhibitor of glioblastoma cell adhesion and migration. Also reported to block thrombin-induced platelet aggregation.	5 mg
JAK3 Inhibitor II	**420104**	**{4-[(3′-Bromo-4′-hydroxyphenyl)amino]-6,7-dimethoxyquinazoline; WHI-P154}** A potent, cell-permeable, reversible, ATP-competitive, and specific inhibitor of JAK3 (IC_{50} = 5.6 µM). Has no effect on either JAK1 or JAK2. Has also been shown to prevent the ionizing radiation-induced activation of c-Jun in DT-40 cells. Also acts as a potent inhibitor of glioblastoma cell adhesion and migration.	5 mg
JAK3 Inhibitor IV	**420121**	**[2-Naphthyl-(N-isopropyl,N-benzyl)-ß-aminoethylketone, HCl; ZM 39923]** A (ß-aminoethyl)ketone that acts as a potent and selective ATP-competitive inhibitor of Janus tyrosine kinase-3 (JAK3; pIC_{50} = 7.1). A weak inhibitor of other tyrosine kinases (pIC_{50} = 5.6 for EGF-R; 4.4 for JAK1). It undergoes a retro-Michael breakdown ($t_{1/2}$ = 36 min at 25˚C, pH 7.43) to another active 2-naphthylvinyl ketone analog (JAK Inhibitor V; Cat. No.420122) [pIC_{50} = 6.8 for JAK3; 5.0 for EGF-R; 4.7 for JAK1].	10 mg
JAK3 Inhibitor V	**420122**	**[(2-Naphthylvinyl Ketone); ZM 449829]** A breakdown product of JAK3 Inhibitor-IV (Cat. No.420121) with similar inhibitory potency (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
JAK3 Inhibitor VI	**420126**	A cell-permeable 3′-pyridyl oxindole compound that acts as a potent and reversible inhibitor of JAK3 (IC_{50} = 27 nM)and displays ~16-fold greater selectivity over JAK2. Binds to the enzyme active site and prevents IL-2-induced cellular phosphorylation of JAK3 and STAT5. Inhibits IL-2-induced cell proliferation (IC_{50} = 760 and 250 nM for mouse CTLL and human T-cells, respectively) and alleviates oxazolone-induced ear odema in mouse with an efficacy comparable to that of Dexamethasone (Cat. No.265005).	5 mg
Lavendustin A	**428150**	**{5-Amino-[(N-2,5-dihydroxybenzyl)-N′-2-hydroxybenzyl]salicylic Acid; RG14355}** A cell-permeable, reversible, and substrate competitive inhibitor of EGF receptor tyrosine kinase (IC_{50} = 11 nM) and $p60^{c\text{-}src}$ (IC_{50} = 500 nM) with little effect on protein kinase A or protein kinase C (IC_{50} > 200 µM). Also inhibits NMDA-stimulated cGMP production (IC_{50} = 30 nM). Exhibits anti-proliferative properties. Suppresses the angiogenic action of vascular endothelial growth factor (VEGF) in rats.	1 mg
Lavendustin C	**234450**	**[Compound 5; 5-(N-2′,5′-Dihydroxybenzyl)aminosalicylic Acid]** A cell-permeable, reversible, substrate competitive, and potent inhibitor of $pp60^{c\text{-}src}$ (IC_{50} = 200 nM) and CaM kinase II (IC_{50} = 200 nM).	1 mg
Lck Inhibitor	**428205**	A cell-permeable pyrrolopyrimidine compound that acts as a potent, reversible, selective, and ATP-competitive inhibitor of Lck (IC_{50} at 5 µM ATP = 64-509 Y^{394}, Lckcd pY^{394}, Src, Kdr and Tie-2, respectively; IC_{50} at 1 mM ATP = 16 µM, 66 nM, 126 nM, 420 nM and 5.18 µM for $Lck_{64\text{-}509}$ Y^{394}, Blk, Fyn, Lyn and Csk, respectively). Only minimally affects the activities of other kinases (IC_{50} = 3.2 µM, > 33 µM, > 50 µM and > 50 µM for EGFR, PKC, CDC2/B and ZAP-70, respectively). Also shown to potently block T-cell receptor-stimulated IL-2 production *in vitro* (IC_{50} < 1-40nm in Jurkat T cells) *in vivo* (ED_{50} = 4 mg/kg in mice, ip.)	1 mg
Lck Inhibitor II	**428206**	**[3-(2-(1H-Benzo[d]imidazol-1-yl)-6-(2-morpholinoethoxy) pyrimidin-4-ylamino)-4-methylphenol]** A cell-permeable, ATP binding site-targeting, tri-substituted pyrimidine that acts as a highly potent Lck (lymphocyte specific kinase) inhibitor (IC_{50} = 3 nM; [ATP] = 10 µM). Shown to block IL-2 release in Jurkat E6-1 T cell line (IC_{50} = 54 nM) stimulated by CD3 cross-linking and PMA.	5 mg

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Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Lck Inhibitor III	**428207**	**{2-(1H-Benzo[d]imidazol-1-yl)-N-(5-methoxy-2-methylphenyl)-6-(2-morpholinoethoxy)pyrimidin-4-amine, hydrate}** A cell-permeable, ATP binding site-targeting, tri-substituted pyrimidine that acts as a Lck (lymphocyte specific kinase) inhibitor (IC_{50} = 867 nM; [ATP] = 10 µM). Shown to block IL-2 release in Jurkat E6-1 T cell line (IC_{50} = 1.27 µM) stimulated by CD3 cross-linking and PMA. Although less potent than Lck Inhibitor II (Cat. No.428206), it exhibits much improved aqueous solubility (27 µg/ml in 50 mM PBS, pH 7.4, ionic strength 0.15 M) and *in vivo* bioavailability (F = 22%, p.o. and i.v. at 10 mg/kg).	5 mg
LFM-A13	**435300**	**[α-Cyano-ß-hydroxy-ß-methyl-N-(2,5-dibromophenyl)propenamide]** A potent, cell-permeable, reversible, substrate competitive, 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). Also inhibits Polo-like kinase in an ATP-competitive manner (IC_{50} = 10 µM and 61 µM for Plx1 and Plk3, respectively), and displays antitumor properties. Does not affect the enzymatic activity of other protein tyrosine kinases, including EGFR, HCK, IRK JAK1, and JAK3 even at concentrations of 278 µM. Enhances the chemosensitivity of BTK-positive B-lineage leukemia cells to ceramide- and vincristine-induced apoptosis.	5 mg
Met Kinase Inhibitor	**448101**	**(3Z)-N-(3-Chlorophenyl)-3-((3,5-dimethyl-4-((4-methylpiperazin-1-yl)carbonyl)-1H-pyrrol-2-yl)methylene)-N-methyl-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide; SU11274** A cell-permeable pyrrole indolinone compound that acts as a potent, reversible, and ATP-competitive inhibitor of Met kinase activity (IC_{50} = 20 nM). Exhibits > 60-fold selectivity over Flk and > 400-fold selectivity over Ron, FGFR-1, c-Src, Cdk2, PDGFRß, EGFR, and Tie-2. Shown to inhibit HGF/SF-stimulated cellular signaling and Met-mediated tumorigenesis in various cancer cell lines.	1 mg
Met/Flt-3/VEGFR2 Tyrosine Kinase Inhibitor	**448103**	**N-(4-(1H-Pyrrolo[2,3-b]pyridin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide** A cell-permeable pyrrolopyridine-pyridone compound that acts as a potent ATP-competitive inhibitor of Met, Flt-3 and VEGFR2 (IC_{50} = 1.9, 4.0 and 27 nM, respectively), while exhibiting much reduced potency against Lck and c-Kit (IC_{50} = 290 and 610 nM, respectively) and little or no activity agaisnt Cdk2/CycE, IGF-1R, InsR, MK-2, PKA, and PKCα (IC_{50} >1 µM). Shown to selectively inhibit the Met-dependent, but not Met-independent, proliferation of gastric carcinoma cultures (IC_{50} = 60 nM vs. >5 µM against GTL-6 and N87 cells, respectively) *in vitro* and effectively abolish GTL-6-derived tumor growth (110% reduction of control tumor mass 39 days after tumor implant) by daily oral dosing (50 mg/kg) in mice *in vivo*.	5 mg
Oxindole I	**499600**	**[3-(1H-Pyrrol-2-ylmethylene)-1,3-dihydroindol-2-one]** A potent, cell-permeable, reversible, ATP-competitive and selective inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinase Flk-1 (fetal liver kinase-1; IC_{50} = 390 nM). Also, to a lesser extent, it inhibits platelet derived growth factor receptor (PDGFR) kinase (IC_{50} = 12 µM). However, it does not affect EGFR, HER2, and IGF-1R even at high concentrations (>100 µM). Also inhibits cyclin D1/Cdk4 enzyme (IC_{50} = 4.9 µM) preferentially over cyclin E/Cdk2 (IC_{50} = 10 µM) and cyclin B/Cdk1 (IC_{50} = 10.2 µM).	10 mg
PD 153035	**234490**	**{AG 1517; 4-[(3-Bromophenyl)amino]-6,7-dimethoxyquinazoline; Compound 32; SU 5271}** An extremely potent, cell-permeamble, reversible, ATP-competitive and specific inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR; IC_{50} = 25 pM; K_i = 6 pM). Rapidly suppresses autophosphorylation of EGFR at low nanomolar concentrations in fibroblasts or in human epidermoid carcinoma cells. Also selectively blocks EGF-mediated cellular processes including mitogenesis, early gene expression, and oncogenic transformation. A 10 mM (500 µg/139 µl) solution of PD 153035 (Cat. No.234491) in DMSO is also available.	1 mg
InSolution™PD 153035	**234491**	A 10 mM (500 µg/139 µl) solution of PD 153035 (Cat. No. 234490) in DMSO.	500 µg
PD 156273	**513032**	**{6-Amino-4-[(3-bromophenyl)amino]-7-(methylamino)quinazoline}** A potent, cell-permeable, reversible, and ATP-competitive inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR; IC_{50} = 690 pM). Also inhibits the growth of primary human tumor cell cultures.	1 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
PD 158780	**513035**	**{4-[(3-Bromophenyl)amino]-6-(methylamino)-pyrido[3,4-d]pyridimine}** A potent, cell-permeable, reversible, ATP-competitive inhibitor of the EGFR tyrosine kinase activity (IC_{50} = 8 pM). Also inhibits heregulin-stimulated autophosphorylation in SK-BR-3 (IC_{50} = 49 nM) and MDA-MB-453 (IC_{50} = 52 nM) breast carcinomas. The inhibition is competitive and results from binding of the inhibitor at the ATP site of the enzymes. Inhibits the LPA-stimulated MAP kinase kinase 1/2 (MKK1/2) activation and EGFR tyrosine phosphorylation in HeLa and NIH 3T3 cells. A 10 mM (500 µg/151 µl) solution of PD 158780 (Cat. No.513036) in DMSO is also available.	500 µg
InSolution™PD 158780	**513036**	A 10 mM (500 µg/151 µl) solution of PD 158780 (Cat. No. 513035) in DMSO.	500 µg
PD 168393	**513033**	**{4-[(3-Bromophenyl)amino]-6-acrylamidoquinazoline}** A potent, cell-permeable, irreversible, ATP-competitive and selective inhibitor of EGF receptor (EGFR) tyrosine kinase activity (IC_{50} = 700 pM). Does not inhibit other protein kinases. Acts by binding to the catalytic domain of the EGFR with a 1:1 stoichiometry and alkylating Cys^{773}. Excellent antitumor agent *in vivo*.	1 mg
PD 174265	**513040**	**{4-[(3-Bromophenyl)amino]-6-propionylamidoquinazoline}** A potent, cell-permeable, reversible, ATP-competitive and selective inhibitor of EGF receptor (EGFR) tyrosine kinase activity (IC_{50} = 450 pM). The reversible nature of this compound makes it a less effective antitumor agent than PD 168393 (Cat. No.513033).	1 mg
InSolution™PD 98059	**513001**	A 5 mg/ml solution of PD 98059 (Cat. No. 513000) in anhydrous DMSO.	1 ml
PDGF Receptor Tyrosine Kinase Inhibitor I	**521230**	**[D-64406; (5-Hydroxy-1H-2-indolyl)(1H-2-indolyl)-methanone]** A cell-permeable *bis*(1H-2-indolyl)-1-methanone compound that acts as a highly selective, ATP-competitive, and reversible inhibitor of platelet-derived growth factor (PDGF) receptor tyrosine kinase (IC_{50} = 200 nM in Swiss 3T3 cells for PDGFR; IC_{50} = 90 nM *in vitro* and 200 nM in PAE cells for PDGFß-R; IC_{50} = 1 µM for PDGFα-R). Also potently inhibits Flt3 (Fms-like tyrosine kinase 3) activity (IC_{50} = 300 nM for hPDGFß-R-mFlt3 & 100 nM in EOL-1 cells). Shown to be only weakly active towards Cdk2/cyclin E, EGFR, ErbB2, FGFR-1, GRK2, JAK-2, PKB/Akt, $PKC_{\alpha,\iota}$, and c-Src kinases (IC_{50} > 10 µM). Sensitizes 32D cells to radiation-induced apoptosis. Inhibits DNA synthesis in stimulated-Swiss 3T3 cells (≤ 30 µM), and proliferation of TEL-Flt3-transfected BA/F3 cells (IC_{50} < 300 nM).	1 mg
PDGF Receptor Tyrosine Kinase Inhibitor II	**521231**	**{(5-Butanoate-1H-2-indolyl)(1H-2-indolyl)-methanone; D-65476; [2-(1H-2-Indolylcarbonyl)-1H-5-indolyl]butanoate}** A cell-permeable *bis*(1H-2-indolyl)-1-methanone compound that acts as a highly selective, ATP-competitive and reversible inhibitor of platelet-derived growth factor (PDGF) receptor tyrosine kinase (IC_{50} = 1.1 µM in Swiss 3T3 cells for PDGFR). Also potently inhibits Flt3 (Fms-like tyrosine kinase 3) activity (IC_{50} = 6.2 µM for hPDGFß-R-mFlt3 and 50 nM in EOL-1 cells). Sensitizes 32D cells to radiation-induced apoptosis and inhibits proliferation of TEL-Flt3-transfected BA/F3 cells (IC_{50} < 300 nM). May also serve as a prodrug form of the Platelet Derived Growth Factor Receptor Tyrosine Kinase Inhibitor I (Cat. No.521230) in cells.	1 mg
PDGF Receptor Tyrosine Kinase Inhibitor III	**521232**	**[4-(6,7-Dimethoxy-4-quinazolinyl)-N-(4-phenoxyphenyl)-1-piperazinecarboxamide]** A cell-permeable piperazinyl-quinazoline carboxamide compound that acts as a potent, ATP-competitive, reversible, and selective inhibitor of PDGF receptor family of tyrosine kinases (IC_{50} = 0.05 µM for α-PDGFR; 0.08 µM for ß-PDGFR; 0.05 µM for c-Kit; 0.23 µM for Flt3). Affects the activities of other kinases only at much higher concentrations (IC_{50} ≥ 30 µM for EGFR, FGFR, Src, PKA & PKC). Reported to block the PDGF-BB induced proliferation of porcine aorta smooth muscle cells (IC_{50} = 0.25 µM).	1 mg
PDGFR Tyrosine Kinase Inhibitor IV	**521233**	**3-Fluoro-N-(6,7-dimethoxy-2,4-dihydroindeno[1,2-c]pyrazol-3-yl)phenylamine** A cell-permeable indenopyrazole compound that displays potent antiproliferative properties in several human tumor cell lines (IC_{50} 50 = 4.2 nM and 45 nM for -ß and -α, respectively) and c-Abl (IC_{50} = 22 nM). Exhibits less activity towards Lck, c-Src, and Fyn (IC_{50} = 100 nM, 185 nM and 378 nM, respectively) and exhibits little or no inhibition toward VEGFR, HER-2, Cdk's-1,-2,-4 &-7, bFGFR-1 and EGFR (IC_{50} = 3.1 µM, > 10 µM, > 10 µM, 45.8 µM and > 100 µM, respectively).	1 mg
PDGFR Tyrosine Kinase Inhibitor V	**521234**	**[N-(4-((6,7-Dimethoxy-4-quinoyl)oxy)phenyl)-N'-(2-methylbenzoyl)thiourea]** A cell-permeable quinolinyl-thiourea compound that acts a potent, ATP-competitive, and reversible inhibitor of PDGFR (IC_{50} = 4 and 7.6 nM in ligand-induced cellular PDGFR phosphorylation and in *in vitro* kinase activity, respectively). Inhibits c-kit receptor only at much higher concentrations (IC_{50} = 434 and 234 nM in receptor phosphorylation and kinase activity, respectively). Shown to potently inhibit neointima formation in a rat carotid artery balloon injury model *in vivo* (30 mg/kg, p.o.).	1 mg

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Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
PDGFR Tyrosine Kinase Inhibitor VI, SU6668	**521235**	**[(Z)-3-(2,4-Dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl)-propionic acid]** A cell-permeable indolinone compound that acts as a potent ATP-competitive inhibitor against RTKs (receptor tyrosine kinases) Kit, PDGFRß, VEGFR2 (Flk-1/KDR), FGFR1 activity *in vitro* (IC_{50} = 0.01, 0.1, 3.9, and 3.8 µM, respectively) and PDGF/VEGF/bFGF-mediated angiogenesis and tumor development *in vivo*. Although initially characterized as an RTK inhibitor, SU6668 is now also known to target ser/thr kinases Aurora A, Aurora B, TBK1 (NAK/T2K), and AMPK (IC_{50} = 0.85, 0.047, 1.4, and 1.8 µM, respectively), as well as non-receptor TKs Lyn and Yes (IC_{50} = 4.3 and 5.8 µM, respectively).	5 mg
PDGFR/VEGFR2 Tyrosine Kinase Inhibitor	**521236**	**[5-Br SU6668; (Z)-3-(2,4-Dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl-5-bromo)-1H-pyrrol-3-yl)-propionic acid]** A cell-permeable, ATP-binding pocket-targeting, 5-bromoindolinone analog of SU6668 (Cat. No.521235) that is equally potent as SU6668 in inhibiting PDGFR (IC_{50} = 60 nM against PDGFRß), while exhibiting more enhanced activity against VEGFR2 and FGFR1 (IC_{50} = 1.73 and 2.05 µM, respectively) in cell-free kinase assays. Inhibits cell proliferation mediated by VEGF, FGF, and PDGFß, but is of little effect against EGF-mediated cell proliferation or EGFR *in vitro* kinase activity.	5 mg
Piceatannol	**527948**	**(*trans*-3,3',4,5'-Tetrahydroxystilbene)** A cell-permeable, substrate competitive and reversible plant metabolite that inhibits the activity of rat liver protein kinase A catalytic subunit (IC_{50} = 3 µM), PKC (IC_{50} = 8 µM), MLCK (IC_{50} = 12 µM). In RBL-2H3 cells, the selective inhibition of Syk by piceatannol results in inhibition of FceR1-mediated signaling. Also inhibits wheat embryo Ca^{2+}-dependent protein kinase (CDPK) (IC_{50} = 19 µM), and $p72^{syk}$ (IC_{50} = 10 µM), a non-receptor tyrosine kinase, relative to Lyn in isolated enzyme preparations. Also possesses anti-leukemic properties. Reported to activate sirtuins and promote the survival of eukaryotic cells.	1 mg
PP1 Analog	**529579**	**{4-Amino-1-*tert*-butyl-3-(1'-naphthyl)pyrazolo[3,4-d]pyrimidine}** A potent, reversible, ATP-competitive, and cell-permeable inhibitor of Src-family tyrosine kinases that is > 800 times more selective for the I338G mutant v-Src (IC_{50} = 1.5 nM) compared to wild-type v-Src (IC_{50} = 1.0 µM). Also inhibits wild-type Fyn (IC_{50} = 600 nM).	1 mg
PP1 Analog II, 1NM-PP1	**529581**	**{4-Amino-1-*tert*-butyl-3-(1'-naphthylmethyl)pyrazolo[3,4-d] pyrimidine; Mutant Kinases Inhibitor II; NM}** A cell-permeable and reversible PP1 analog (Cat. No.529579) that acts as a potent and selective ATP-competitive inhibitor of mutant kinases over wild-type (IC_{50} = 3.2 nM for T339G, c-Fyn-as1 vs. 1.0 µM for c-Fyn; 4.3 nM for I338G, v-src-as1 vs. 28 µM for v-src; 5 nM for F80G, CDK2-as1 vs. 29 µM for CDK2; 8 nM for F89G, CAMK IIα-as1 vs. 24 µM for CAMKII; 120 nM for T315A, c-Abl-as2 vs. 3.4 µM for c-Abl). Shown to activate mutants of Ire1, a transmembrane kinase.	1 mg
PP2	**529573**	**{AG 1879; 4-Amino-5-(4-chlorophenyl)-7-(*t*-butyl)pyrazolo[3,4-d]pyrimidine}** A potent, reversible, ATP-competitive, and selective inhibitor of the Src family of protein tyrosine kinases. Inhibits $p56^{lck}$ (IC_{50} = 4 nM), $p59^{fynT}$ (IC_{50} = 5 nM), Hck (IC_{50} = 5 nM), and Src (IC_{50} = 100 nM). Does not significantly affect the activity of EGFR kinase (IC_{50} = 480 nM), JAK2 (IC_{50} > 50 µM), or ZAP-70 (IC_{50} >100 µM). Inhibits the activation of focal adhesion kinase and its phosphorylation at Tyr^{577}. Also potently inhibits anti-CD3-stimulated tyrosine phosphorylation of human T cells (IC_{50} = 600 nM). A 10 mM (1 mg/331 µl) solution of PP2 (Cat. No.529576) in DMSO also available.	1 mg
InSolution™PP2	**529576**	A 10 mM (1 mg/331 µl) solution of PP2 (Cat. No. 529573) in DMSO.	1 mg
PP3	**529574**	**(4-Amino-7-phenylpyrazol[3,4-d]pyrimidine)** A negative control for the Src family protein tyrosine kinase inhibitor PP2 (Cat. No.529573). However, it inhibits the activity of EGFR kinase (IC_{50} = 2.7 µM).	1 mg
Radicicol, *Diheterospora chlamydosporia*	**553400**	A cell-permeable, ATP-site binding, and irreversible antifungal macrocyclic lactone antibiotic that acts as a protein tyrosine kinase inhibitor. Inhibits $p60^{v\text{-}src}$ kinase activity (IC_{50} = 0.27 nM). Inhibits the expression of COX-2 (IC_{50} = 27 nM) without affecting COX-1 expression in LPS-stimulated macrophages. Disrupts K-Ras-activated signaling pathways by selectively depleting Raf kinase. Inhibits tyrosine phosphorylation of $p53/56^{lyn}$ in LPS-stimulated macrophages. Suppresses NIH/3T3 cell transformation by diverse oncogenes such as *src*, *ras*, and *mos* in part by blocking the key signal transduction intermediates such as MAP kinase and GAP-associated p62. Also exhibits anti-angiogenic activity *in vivo*. Inhibits Wnt-5A expression in dermal papilla cells (IC_{50} = 190 nM).	500 µg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
RET Receptor Tyrosine Kinase Inhibitor	**554340**	**[RPI-1; 1,3-Dihydro-5,6-dimethoxy-3-((4-hydroxyphenyl)methylene)-2H-indol-2-one]** A cell-permeable, indolinone-based ATP-competitive tyrosine kinase inhibitor that is known to target Ret (IC_{50} = 170 nM), EGFR, and Met. Selectively reverts the morphologic phenotype of ret oncogene- (PTC1 & MEN2A), but not H-Ras-, transformed NIH3T3 in a reversible manner. RPI-1 effectively inhibits the autophosphorylation of PTC1, MEN2A, and Met (IC_{50} against Met $Tyr^{1234/1235}$ in N592 ≤7.5 µM) in cancer cells, and concomitant receptor down-regulation has also been reported to occur in $NIH3T3^{MEN2A}$ and in small cell lung carcinoma cell line N592. Orally available in mice and is efficacious in inhibiting MEN2A- and Met-mediated tumorigenesis both *in vitro* (IC_{50} against $NIH3T3^{MEN2A}$ and TT proliferation = 3.6 and 7.2 µM, respectively) and in various murine xenograft models *in vivo* (50 to 150 mg/kg, b.i.d.).	10 mg
Src Family Protein Tyrosine Kinase Inhibitor Set	**567816**	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).	1 set
Src Kinase Inhibitor I	**567805**	**[4-(4'-Phenoxyanilino)-6,7-dimethoxyquinazoline]** A 4'-phenoxy substituted 4-anilinoquinazoline compound that acts as a potent, selective, dual site, cell-permeable, reversible and ATP-competitive inhibitor of Src family tyrosine kinases (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 at much higher concentrations (IC_{50} = 0.32 µM and 30 µM, respectively).	1 mg
Src Kinase Inhibitor II	**567806**	A substituted triazoloquinoline-1-thione compound that acts as a potent, ATP-competitive, reversible and selective inhibitor of Src family tyrosine kinases (IC_{50} = 1.2 µM for human recombinant Csk). Exhibits little effect against p38 MAPK or FGFR even at concentrations as high as 50 µM.	5 mg
ST638	**567790**	**[α-Cyano-(3-ethoxy-4-hydroxy-5-phenylthiomethyl)cinnamide]** A cell-permeable, reversible, and substrate competitive protein tyrosine kinase inhibitor (IC_{50} = 370 nM) that also inhibits HGF-induced MAP kinase activation in hepatocytes. Also shown to inhibit phospholipase D activity in human neutrophils. Decreases the O_2^- production induced by pervanadate in guinea pig neutrophils.	5 mg
Staurosporine, N-Benzoyl	**539648**	**(CGP 41 251; N-Benzoylstaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derivative that displays antitumor properties. Acts as a broad-spectrum, reversible, and ATP-competitive inhibitor of PKC (α, ß and γ), PDGFRß, VEGFR2, Syk, PKCη, PKCδ, Flk-1, Flt3, Cdk1/B, PKA, c-Kit, c-Fgr, c-Src, VEGFR1, and EGFR (IC_{50} = 22 nM, 50 nM, 86 nM, 95 nM, 160 nM, 330 nM, 390 nM, 528 nM, 570 nM, 570 nM, 600 nM, 790 nM, 800 nM, 912 nM, and 1.0 µM, respectively). At higher concentrations, also inhibits Ins-R and IGF-1R (IC_{50} = 10 &tmicroM). Shown to potently inhibit the proliferation of Ba/F3 cells expressing constitutively active Flt3 (IC_{50} < 10 nM).	1 mg
Ste11 MAPKKK Activation Inhibitor	**570100**	**[4-((2,4-Dichlorophenyl)amino)-6,7-dimethoxyquinazoline]** AA quinazolinamine PD 153035 (Cat. No.234490) analog that inhibits Ste11 signaling and c-Abl tyrosine kinase activity in yeast. Also reported to inhibit Src kinase activity with an IC_{50} of 250 nM.	5 mg
Stem-Cell Factor/c-Kit Inhibitor, ISCK03	**569615**	**[SCF/c-Kit Signaling Inhibitor, ISCK03; 4-t-Butylphenyl-N-(4-imidazol-1-yl-phenyl)sulfonamide]** A cell-permeable phenyl-imidazolosulfonamide compound that inhibits c-kit activity (IC50 90% inhibition) without any effect on HGF-induced Erk phosphorylation in 501mel melanoma cells. Oral administration of ISCK03 is shown to induce hair depigmentation in C57BL/6 mice in a dose-dependent and reversible manner. Topical application is likewise demonstrated to decrease UV-induced pigmentation and epidermal melanin level in Brownish guinea pigs *in vivo*.	10 mg
SU11652	**572660**	**{5-[(Z)-(5-Chloro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-N-[2-(diethylamino)ethyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide}** A cell-permeable pyrrole-indolinone compound that acts as a potent, reversible, and ATP-competitive tyrosine kinase receptor and angiogenic inhibitor that exhibits greater selectivity for PDGFRß (IC_{50} = 3 nM), VEGFR2 (IC_{50} = 27 nM), FGFR1 (IC_{50} = 170 nM), and Kit family members (IC_{50} = ~ 10-500 nM) over EGFR (IC_{50} >20 µM). Reported to display anti-proliferative and pro-apoptotic properties in tumor cells.	500 µg
SU1498	**572888**	**{(E)-3-(3,5-Diisopropyl-4-hydroxyphenyl)-2-[(3-phenyl-n-propyl) amino-carbonyl]acrylonitrile}** A potent, reversible, ATP-competitive and selective inhibitor of Flk-1 kinase (IC_{50} = 700 nM), a vascular endothelial growth factor (VEGF) receptor kinase. Also reduces the expression of *ets-1*, a transcription factor stimulated by VEGF. Has only a weak inhibitory effect on PDGF-receptor (IC_{50} >50 µM), EGF-receptor (IC_{50} >100 µM), and HER2 (IC_{50} >100 µM) kinases. Acts as an angiogenesis inhibitor as shown by its activity in the chorioallantoic membrane (CAM) assay and in an *in vivo* VEGF-induced permeability assay.	5 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
SU4984	**572625**	**{3[4-(1-Formylpiperazin-4-yl)benzylidenyl]-2-indolinone}** A cell-permeable, reversible, and ATP-competitive inhibitor of the tyrosine kinase activity of fibroblast growth factor receptor 1 (FGFR1; IC_{50} = 10-20 µM in the presence of 1 mM ATP). Also inhibits aFGF-induced tyrosine phosphorylation of ERK1 and ERK2 (IC_{50} = 20-40 µM) and the tyrosine phosphorylation of the PDGF receptor and the insulin receptor. Does not inhibit the kinase activity of the EGF receptor.	1 mg
SU5402	**572630**	**{3-[3-(2-Carboxyethyl)-4-methylpyrrol-2-methylidenyl]-2-indolinone}** A cell-permeable, reversible, and ATP-competitive inhibitor of the tyrosine kinase activity of fibroblast growth factor receptor 1 (FGFR1; IC_{50} = 10-20 µM in the presence of 1 mM ATP). Also inhibits aFGF-induced tyrosine phosphorylation of ERK1 and ERK2 (IC_{50} = 10-20 µM). In contrast to SU4984 (Cat. No.572625), SU5402 is only a weak inhibitor of tyrosine phosphorylation of the PDGF receptor and does not inhibit phosphorylation of the insulin receptor. Does not inhibit the kinase activity of the EGF receptor. A 10 mM (500 µg/169 µl) solution of SU5402 (Cat. No.572631) in DMSO is also available.	500 µg
InSolution™SU5402	**572631**	A 10 mM (500 µg/169 µl) solution of SU5402 (Cat. No. 572630) in DMSO.	500 µg
SU5614	**572632**	**{5-Chloro-3-[(3,5-dimethylpyrrol-2-yl)methylene]-2-indolinone}** A potent, cell-permeable, reversible, ATP-competitive, and selective inhibitor of VEGF (Flk-1; IC_{50} = 1.2 µM) and PDGF (IC_{50} = 2.9 µM) receptor tyrosine kinases. Does not have any effect on the EGF and IGF receptor tyrosine kinases. Also inhibits the VEGF-driven mitogenesis of human umbilical vein endothelial cells (HUVECs; $IC_{50} \leq$ 680 nM). Inhibits Flt3 phosphorylation in Flt3/Itd-BaF3 cells.	1 mg
SU6656	**572635**	A potent, cell-permeable, reversible, and ATP-competitive Src family kinase inhibitor. Inhibits Src (IC_{50} = 280 nM) as well as closely related kinases such as Fyn (IC_{50} = 170 nM) and Yes (IC_{50} = 20 nM) and Lyn (IC_{50} = 130 nM). Acts as a weak inhibitor of Lck (IC_{50} = 688 µM) and PDGF receptor kinase (IC_{50} >10 µM). A 10 mM (500 µg/135 µl) solution of SU6656 (Cat. No.572636) in DMSO is also available.	1 mg
InSolution™SU6656	**572636**	A 10 mM (500 µg/135 µl) solution of SU6656 (Cat. No. 572635) in DMSO.	500 µg
Syk Inhibitor	**574711**	**[3-(1-Methyl-1H-indol-3-yl-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonamide; Spleen Tyrosine Kinase Inhibitor]** A cell-permeable oxindole compound that acts as a potent, reversible, and ATP-competitive Syk inhibitor (IC_{50} = 14 nM). Has been shown to effectively inhibit FcRI-mediated degranulation in the rat basophilic leukemia cell line, RBL-2H3 (EC_{50} = 313 nM).	5 mg
Syk Inhibitor II	**574712**	**2-(2-Aminoethylamino)-4-(3-trifluoromethylanilino)-pyrimidine-5-carboxamide, Dihydrochloride** A cell-permeable pyrimidine-carboxamide compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of Syk (IC_{50} = 41 nM), while affecting PKC, $PKC_{\beta II}$, ZAP-70, Btk, and Itk only at much higher concentrations (IC_{50} = 5.1, 11, 11.2, 15.5, and 22.6 µM, respectively). Inhibits FcRI-mediated 5-HT release in RBL-2H3 cells *in vitro* (IC_{50} = 460 nM) and passive cutaneous anaphylaxis (PCA) reaction in mice *in vivo* (ID_{50} = 13.2 mg/kg, s.c.).	1 mg
Syk Inhibitor III	**574713**	**(3,4-Methylenedioxy-ß-nitrostyrene)** A cell-permeable nitrostyrene compound that acts as a selective inhibitor of Syk kinase activity (IC_{50} = 2.5 µM). It inhibits Src only at much higher concentrations (IC_{50} = 29.3 µM) and exhibits little effect against Fak and JAK2. Shown to potently inhibit platelet aggregation induced by various stimulators, including U46619, ADP, arachidonic acid, collagen, thrombin, ionophore A23187, and PDBu (IC_{50} ranges from 2.1 to 25.9 µM).	50 mg
Syk Inhibitor IV	**574714**	**{BAY 61-3606; 2-(7-(3,4-Dimethoxyphenyl)-imidazo[1,2-c] pyrimidin-5-ylamino)-nicotinamide, HCl}** A cell-permeable imidazopyrimidine compound that acts a potent, ATP-competitive, reversible, and highly selective inhibitor of Syk tyrosine kinase activity (IC_{50} = 10 nM) with no inhibitory effect against Btk, Fyn, Itk, Lyn, and Src even at concentrations as high as 4.7 µM. Shown to inhibit Syk-mediated cellular functions *in vitro* and exhibit good oral bioavailability and *in vivo* effacacy in the treatment of various allgery and asthma conditions in rat models.	2 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
(-)-Terreic Acid, Synthetic	**581810**	**{(1R,6S)-3-Hydroxy-4-methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione}** A cell-permeable quinone epoxide antibiotic that acts as a reversible, substrate competitive, and selective inhibitor of Bruton's tyrosine kinase catalytic activity (BTK; IC_{50} = 10 µM and 3 µM for the basal and activation levels). Shown to bind to the BTK pleckstrin homology domain (BTK-PH) and block the interaction between the BTK-PH and PKC (IC_{50} = ~ 100 µM in human mast cell lysates), thus affecting the catalytic activity of BTK, but not of PKC. Selectively inhibits the autophosphorylating activity of $PKC_{\beta I}$ (IC_{50} = ~ 8 µM) and not of $PKC_{\beta II}$. Reported to effectively inhibit the production of TNF-α (IC_{50} = ~ 3 µM), and activation of JNK1 (IC_{50} = ~ 10 µM) in FcRI-stimulated mast cells. Also inhibits the DNA synthesis in activated spleen cells (IC_{50} = ~ 1.5 µM). Does not significantly affect the activities of Lyn, Syk, PKA, CK-1, ERK1, ERK2, and p38 kinases.	2 mg
2'-Thioadenosine	**589400**	**(PD 157432)** A cell-permeable, potent, selective, ATP-competitive and irreversible inhibitor of the catalytic domain of the ErbB subfamily of protein tyrosine kinases. Inactivates ErbB1 (epidermal growth factor receptor) modifying the cysteine residue Cys^{797} at the active site. This inactivation is reversed with the addition of 1 mM DTT. Also inhibits ErbB2 (Neu/Her2 growth factor receptor; IC_{50} = 45 µM). This product is very unstable when exposed to oxygen. Unstable in solution; reconstitute just prior to use.	2 mg
Tie2 Kinase Inhibitor	**612085**	**[4-(6-Methoxy-2-naphthyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole]** A cell-permeable pyridinylimidazole compound that acts as a potent, reversible, and ATP-binding site-targeting inhibitor of Tie2 (IC_{50} = 250 nM) with ~ 200-fold selectivity over p38 MAPK and greater than 10-fold selectivity over VEGFR2, VEGFR3, and PDGFR1ß. Shown to exhibit antiangiogenesis activity in a Matrigel assay (70% reduction, 50 mg/kg/0.5 day, i.p.) and inhibit the growth of xenografted tumor (no apparent growth up to 20 days, 25 mg/kg/0.5 day, i.p.) in mice *in vivo*.	5 mg
TrkA Inhibitor	**648450**	An oxindole compound that acts as a cell-permeable, reversible, potent, and highly selective inhibitor of TrkA (IC_{50} = 63 nM), presumably by targeting the kinase's ATP binding pocket. Shown to exhibit ≥150-fold selectivity over Cdk1 and cRaf1.	1 mg
TX-1123	**655200**	**[2-((3,5-di-*tert*-Butyl-4-hydroxyphenyl)-methylene)-4-cyclopentene-1,3-dione]** A cell-permeable, reversible, and substrate-competitive arylidene-cyclopentenedione derived tyrphostin that acts as an inhibitor for Src, eEF2-K, and PKA (IC_{50} = 2.2, 3.2, and 9.6 µM, respectively), while it inhibits EGFR-K and PKC at much higher concentrations (IC_{50} = 320 µM). Displays potent antitumor activity (EC_{50} = 3.66 and 39 µM in HepG2 and HCT116 tumor cells, respectively) with greatly reduced mitochondrial- (≥1000-fold) and hepato-toxicity (≥50-fold) when compared with another tyrphostin, AG 17 (Cat. No.658425). It is therefore a more promising candidate as a therapeutic agent for cancer treatment.	10 mg
Tyrene CR4	**655230**	A cell-permeable, reversible, and substrate competitive hydroxystryrylacrylonitrile tyrosine kinase inhibitor that displays anti-tumor properties. Potently inhibits the kinase activities of JAK2 and Bcr-Abl (IC_{50} = ~100-600 nM and 500-700 nM, respectively), and displays excellent selectivity over other tyrosine kinases, Btk, Lck, Lyn, Src, Syk and ZAP-70 (IC_{50} >5 µM). Shown to preferentially induce apoptosis in acute lymphoblastic (ALL) and myeloid leukemia cells (AML), while exhibiting little deleterious effect towards normal bone marrow cell differentiation and proliferation. Reported to be much more potent than AG 490 (Cat. No.658401) in inducing ALL cells growth arrest (IC_{50} = ~120 nM vs. 5-25 µM). Its *in vivo* efficacy in cancer reduction has been successfully demonstrated in NOD-SCID mice engrafted with human Ph^+ ALL cells.	5 mg
Tyrosine Kinase Inhibitor Set II	**657021**	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). Supplied with an informational insert.	1 set
UCN-01	**539644**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp; 7-Hydroxystaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derived anticancer agent that reversibly and ATP-competitively inhibits several protein kinases (IC_{50} = 29 nM, 34 nM, 30 nM, 590 nM and 530 nM for PKCα, PKCß, PKCγ, PKCδ and PKC; IC_{50} = 7 nM, 27 nM, 50 nM, 50 nM, 150 nM and 1.04 µM for Chk1, Cdc25C-associated protein kinase 1, Cdk1, PAK4, Cdk5/p25 and Chk2; IC_{50} = 33 nM, 50 nM, 95 nM, 500 nM, 500 nM and 1.0 µM for PDK1, lck, MAPKAP kinase-2, Akt, GSK-3ß and PKA, respectively). At higher concentrations (> 15 µM), affects the activities of Src, PIM-1, CKII, DNA-PK, ErK1, ILK-1 and MAPKK1). Reported to suppress thymidylate synthase expression, induce apoptosis with caspase activation, and sensitize tumor cells to a range of DNA-damaging agents.	500 µg
UCN-02	**539645**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp.; 7-epi-Hydroxystaurosporine)** A cell-permeable ATP-competitive PKC inhibitor that exhibits decreased potency and selectivity towards calcium-dependent isoforms (IC_{50} = 0.53, 0.7, 0.39, 2.83, and 1.23 µM for PKCα, PKCß, PKCγ, PKCδ, and PKC, respectively) when compared with its stereoisomer UCN-01 (Cat. No.539644). Does not inhibit PKCζ even at concentrations as high as 10 µM.	500 µg

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Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
VEGF Inhibitor, CBO-P11	**676496**	**cyclic(*D*-F-PQIMRIKPHQGQHIGE)** A macrocyclic 17-amino acid peptide derived from residues 79 - 93 of vascular endothelial growth factor that mediate its binding to VEGFR-2. It blocks the binding of $VEGF_{165}$ to its receptors (IC_{50} = 700 nM for VEGFR1, 1.3 µM for VEGFR2) and exhibits anti-angiogenic activity as well as other VEGFR-mediated cellular functions, such as proliferation (IC_{50} = 5.8 µM), migration (IC_{50} = 8.2 µM), and activation of MAP kinases. Its anti-angiogenic activity has been successfully demonstrated *in vivo* using chick embryos and nude mice tumor models of human intracranial and syngeneic glioma.	1 mg
VEGF Inhibitor, Flt_{2-11}	**676493**	**NITVTLKKFPL** An 11-amino acid peptide derived from the second Ig-like domain of vascular endothelial growth factor receptor-1 (VEGFR-1 or Flt-1) that is shown to inhibit angiogenesis in chick chorioallantoic membrane and inhibits VEGF-induced vascular permeability. Neither binds to vascular endothelial growth factor (VEGF) nor inhibits its binding to VEGFR. Reported to form a stable ß-sheet structure and exists as a dimer in solution.	1 mg
VEGF Inhibitor, Je-11	**676494**	**$(RTELNVGIDFNWEYPAS)_2K\text{-}NH_2$** A dimerized peptide derived from the third Ig-like domain of the human vascular endothelial growth factor receptor-2 (VEGFR-2 or KDR/Flk-1) comprising residues 247 - 261. Acts as an inhibitor of VEGF-stimulated autophosphorylation of VEGFR-2 and inhibits the proliferation and migration of cultured microvascular endothelial cells. Binds to VEGF and blocks its interaction with VEGFR-2 (IC_{50} = 500 nM on extracellular VEGFR-2 fragments; IC_{50} = 30 µM on HUVEC).	1 mg
VEGF Inhibitor, V1	**676495**	**ATWLPPR** An NRP-1-binding heptapeptide whose target was initially mistaken as VEGFR2/KDR/Flk-1 due to its binding activity to a CHO-KDR culture that was later shown to express primarily NRP-1 and little KDR. V1/A7R specifically competes against $VEGF_{165}$ binding to recombinant NRP-1 in cell-free binding assays (IC_{50} = 60 µM), while exhibiting no activity against the interaction between NRP-1 and heparin or $VEGF_{165}$ binding to KDR, VEGFR1/Flt-1, and heparin. V1/A7R is demonstrated to inhibit VEGF-dependent angiogenesis activity in HMVEC (IC_{50} = 0.3 µM) and HUVEC cultures *in vitro*, as well as in a rabbit corneal neovascularization model and in mice bearing MDA-MB-231-derived tumor *in vivo*.	1 mg
VEGF Receptor 2 Kinase Inhibitor I	**676480**	**{(*Z*)-3-[(2,4-Dimethyl-3-(ethoxycarbonyl)pyrrol-5-yl)methylidenyl]indolin-2-one}** A highly selective, cell-permeable, reversible, and ATP-competitive 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. Does not inhibit PDGF, EGF, and IGF-1 RTK activities (IC_{50} > 100 µM).	1 mg
VEGF Receptor 2 Kinase Inhibitor II	**676485**	**[(*Z*)-5-Bromo-3-(4,5,6,7-tetrahydro-1*H*-indol-2-ylmethylene)-1,3-dihydroindol-2-one]** A membrane permeant and reversible indolin-2-one class of receptor tyrosine kinase (RTK) inhibitor [IC_{50} = 70 nM for VEGF-R2 (KDR/Flk-1), 920 nM for PDGF-Rß, 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. Does not inhibit EGF-R kinase activity (IC_{50} > 100 µM).	1 mg
VEGF Receptor 2 Kinase Inhibitor III	**676487**	**{3-[(2,4-Dimethylpyrrol-5-yl)methylidene]-indolin-2-one; SU5416}** A cell-permeable indolinone compound that acts as a selective, reversible, and ATP-competitive inhibitor of VEGF-R (KDR/Flk-1) and PDGF-R tyrosine kinases (IC_{50} = 1.04 µM and 20 µM in NIH 3T3 cells overexpressing Flk-1; K_m = 530 nM for ATP). Also potently inhibits the proliferation of HUVECs induced by VEGF, bFGF, or ECGS (IC_{50} = 50 nM, 5.3 µM and 30.5 µM, respectively). Blocks the autophosphorylation of internal tandem duplication (ITD) and wild type Fms-like tyrosine kinase 3 (FLT3) with an IC_{50} of 0.1 µM. Does not affect the EGF- or FGF- receptor tyrosine kinases activities even at 100 µM concentration. Reported to induce apoptosis and inhibit VEGF-dependent mitogenesis of human endothelial cells. A 10 mM (500 µg/210 µl) solution of VEGF Receptor 2 Kinase Inhibitor III (Cat. No.676498) in DMSO is also available.	1 mg
InSolution™VEGF Receptor 2 Kinase Inhibitor III	**676498**	A 10 mM (500 µg/210 µl) solution of VEGF Receptor 2 Kinase Inhibitor III (Cat. No. 676487) in DMSO.	500 µg
VEGF Receptor 2 Kinase Inhibitor IV	**676489**	**{KDR/Flk-1 Kinase Inhibitor IV; 3-(3-Thienyl)-6-(4-methoxyphenyl)pyrazolo [1,5-*a*]pyrimidine}** A 3,6-diaryl substituted pyrazolopyrimidine that acts as a potent, reversible, and ATP-competitive inhibitor of VEGFR-2 (KDR/Flk-1; IC_{50} = 19 nM). Displays ~2-fold greater selectivity for VEGFR-2 over PDGFRß (IC_{50} = 34 nM) and 10-fold greater selectivity over VEGFR-1 (Flt-1) and VEGFR-3 (Flt-4; IC_{50} = 190 nM) tyrosine kinase activity. Does not inhibit FGFR-1 or Src kinase activity (IC_{50} > 1.9 µM). Shown to inhibit VEGF-stimulated mitogenesis in human umbilical vein endothelial cells (IC_{50} = 387 nM). Inhibits Flt3 phosphorylation in Flt3/Itd-BaF3 cells.	1 mg

Protein Tyrosine Kinase (PTK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
VEGF Receptor 2 Kinase Inhibitor VI	**676484**	**[Ki8751; N-(2,4-Difluorophenyl)-N'-(4-(6,7-dimethoxy-4-quinolyloxy)-2-fluorophenyl)urea]** A cell-permeable quinolyloxyphenyl-urea compound that acts as a VEGFR-2-selective inhibitior in both cell-based (IC_{50} = 0.9 nM in VEGF-induced receptor phosphorylation) and cell-free (IC_{50} = 4.0 nM in kinase reactions) assays. It inhibits c-Kit, PDGFRα, and FGFR-2 only at much higher concentrations (IC_{50} = 40, 67, and 170 µM, respectively, in cell-based assays), while exhibiting no effect against eight other commonly studied receptor and non-receptor kinases even at concentrations as high as 10 µM. Effectively blocks VEGF-dependent, but not VEGF-independent, cell proliferation *in vitro* and tumor growth in mice and rats (5 to 20 mg/kg, daily p.o.) *in vivo*.	5 mg
VEGF Receptor 2/Flt3/c-Kit Inhibitor	**676500**	**[N-(4-(3-Amino-1H-indazol-4-yl)phenyl)-N'-(3-methylphenyl)urea]** A cell-permeable 3-aminoindazolylurea compound that acts as a potent and ATP-competitive inhibitor of VEGFR2/KDR (IC_{50} = 3 nM) as well as Flt3 and cKit (IC_{50} = 4 to 20 nM). Shown to block VEGF-induced VEGFR2 phosphorylation in 3T3-murine fibroblasts *in vitro* (IC_{50} = 13 nM) and exhibit oral availability (AUC = 6.5 µM•h with an oral dose of 10 mg/kg in CD-1 mice) and *in vivo* efficacy in a murine estradiol-induced uterine edema model (ED_{50} = 4 mg/kg p.o. in balb/c mice).	5 mg
VEGF Receptor 3 Kinase Inhibitor, MAZ51	**676492**	**[3-(4-Dimethylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one; MAZ51]** A cell-permeable 3-substituted indolin-2-one compound that acts as a reversible and ATP-competitive VEGF receptor tyrosine kinase inhibitor. At low concentration (≤5 µM), it specifically blocks VEGF-C- (Cat. No.676476) and VEGF-D- (Cat. No.676471) induced phosphorylation of VEGFR-3, but not VEGFR-2, in PAE cells. It partially blocks VEGFR-2 phosphorylation only at higher concentrations (50 µM). This differential blocker may be useful for inhibiting lymphangiogenesis-dependent pathological process such as tumor metastasis. *Not available for sale in Germany.*	10 mg
VEGF Receptor Tyrosine Kinase Inhibitor II	**676481**	**{N-(4-Chlorophenyl)-2-[(pyridin-4-ylmethyl)amino]benzamide}** A pyridinyl-anthranilamide compound that displays both antiangiogenic and antitumor properties. A potent, cell-permeable, reversible, and ATP-competitive inhibitor of the kinase activities of KDR, Flt-1 and c-Kit (IC_{50} = 20 nM, 180 nM and 240 nM, respectively), and minimally inhibit c-Src and EGF-R activities (IC_{50} = 7 µM and 7.3 µM). Further, inactive towards the inhibition of CDK-1, c-Met, IGF-1R and PKA (IC_{50} > 10 µM).	5 mg
VEGF Receptor Tyrosine Kinase Inhibitor IV	**676483**	**[N-(2-Chloro-4-((6,7-dimethoxy-4-quinolyl)oxy) phenyl)-N'-(5-methyl-3-isoxazolyl)urea]** A cell-permeable quinoline-urea compound that potently inhibits the kinase activity of VEGFR (IC_{50} = 30, 6.5, and 15 nM for VEGFR-1,-2,and -3, respectively), EphB2, PDGFR-α, PDGFR-ß, c-Kit, and Tie-2 (IC_{50} = 24, 40, 49, 78, and 78 nM, respectively). It exhibits little or no activity towards a panel of 15 other tyrosine kinases, including FGFR, IR, and IGFR, in cell-free kinase assays, while showing more than 7-fold higher potency in inhibiting ligand-induced phosphorylation of VEGFR-1/2/3 vs. c-Kit, PDGFR-ß, Flt3, FGFR1, and c-Met in cell-based assays. Shown to be orally available and suppress tumor angiogenesis and growth in rats *in vivo*.	500 µg
VEGF Receptor Tyrosine Kinase Inhibitor V	**676501**	**[N-Cyclopropyl-6-(6,7-dimethoxyquinolin-4-yloxy)-1-naphthamide, HCl]** A cell-permeable, ATP-binding pocket-targeting N-cyclopropylnaphthamide compound that acts as a potent inhibitor against VEGFR1/2/3 (IC_{50} = 0.6 nM against VEGFR2), c-FMS, RET, Lyn, and c-KIt, while exhibiting much reduced activity against 36 other commonly studied kinases. Selectively inhibits HUVEC proliferation induced by VEGF over bFGF (IC_{50} = 0.91 vs. 170 nM, respectively). It is orally active in mice and rats and is shown to effectively reduce VEGF-mediated vascular permeability and angiogenesis *in vivo*.	5 mg

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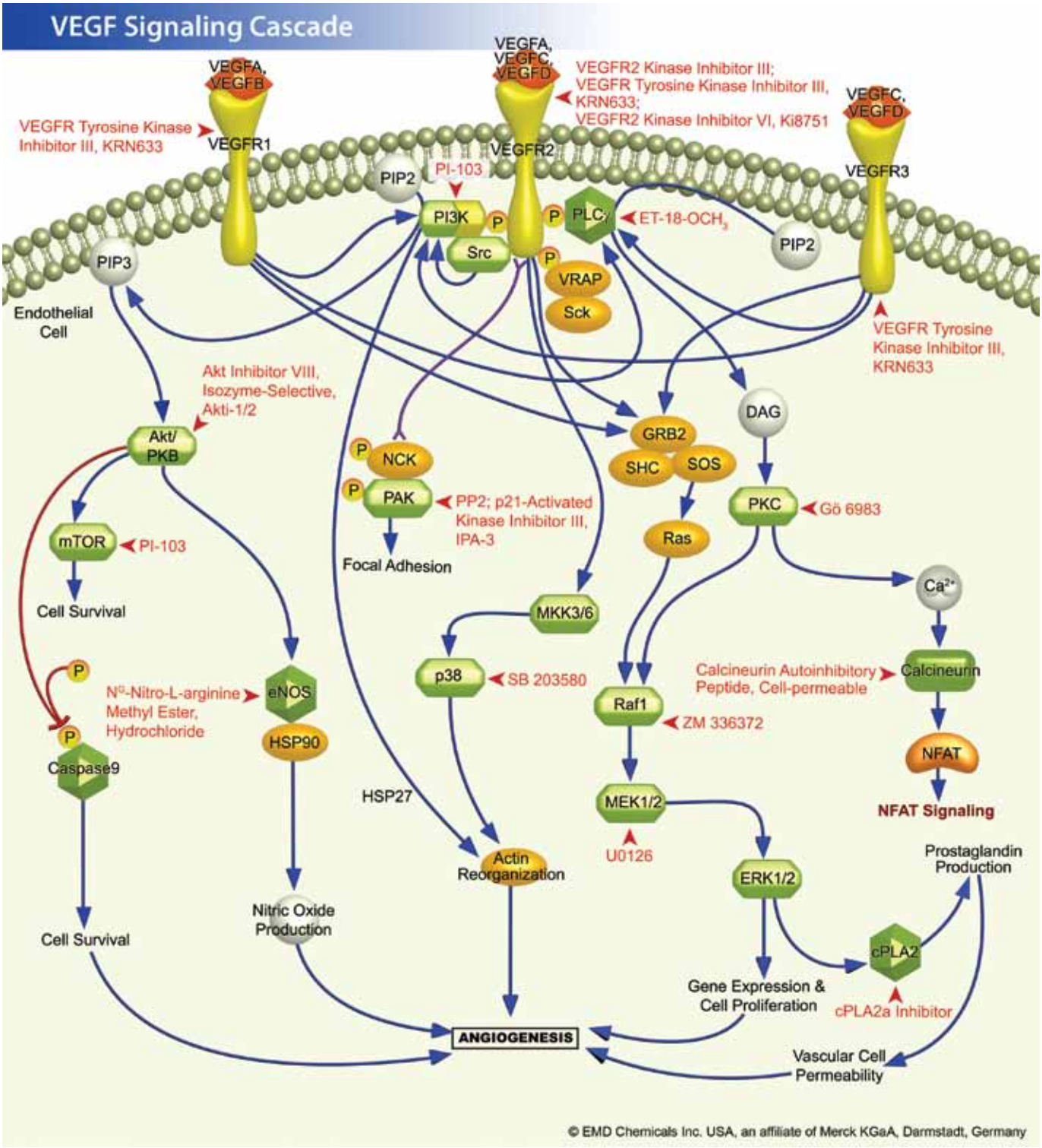
Highlighted below are inhibitors included in InhibitorSelect™ VEGF Signaling Pathway Inhibitor Panel (Cat. No. 676502). See page 205 for details.



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. More recently, c-Raf inhibitors have been considered as protective agents against β-amyloid toxicity.

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Raf Kinase Inhibitors

Product	Cat. No.	Comments	Size
Raf Kinase Inhibitor IV	**553014**	**[L 779450; 2-(Phenyl)-4-(3-hydroxy-4-chlorophenyl)-5-(4-pyridyl)-1H-imidazole]** A cell-permeable triarylimidazole compound that acts as a reversible, ATP-competitive, and highly potent inhibitor of Raf kinase (IC_{50} = 10 nM and K_d = 2.4 nM for B-raf) with 7-, 30-, and 70-fold selectivity over p38α, GSK-3ß, and Lck, respectively. Cellular data have indicated that the compound is more effective towards Raf-1and A-Raf than B-Raf.	1 mg
Raf Kinase Inhibitor V	**553015**	**PLX4720** A cell-permeable azaindole compound that interacts with Raf via both the ATP-binding site and a "Raf-selective pocket" that exhibits conformation-dependent inhibitor-binding modes and accounts for the compound's preferential binding and inhibitory activity toward the active Raf mutants (IC_{50} = 6.7, 13, 130, 160, and >1,300 nM against C-Raf-1$^{Y340D/Y341D}$, B-Raf^{V600E}, BRK, WT B-Raf, and 64 other kinases, respectively). Shown to inhibit the proliferation and cellular Erk phosphorylation much more potently in B-Raf^{V600E}-bearing than WT B-Raf-bearing cancer cell lines *in vitro* and effectively suppress COLO205-derived tumor growth in mice *in vivo* (near complete regression during the 1-wk treatment period; 20 mg/kg, daily, p.o.).	1 mg
InSolution™Raf1 Kinase Inhibitor I	**553003**	A 10 mM (500 µg/96 µl) solution of Raf1 Inhibitor I (Cat. No. 553008) in DMSO.	500 µg
Raf1 Kinase Inhibitor I	**553008**	**{5-Iodo-3-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-indolinone}** A potent, cell-permeable, reversible, and ATP-competitive cRAF1 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. Predicted broad spectrum antitumor agents. A 10 mM (500 µg/96 µl) solution of Raf1 Inhibitor I (Cat. No.553003) in DMSO is also available.	1 mg
Rb/Raf-1 Disruptor 251	**559270**	**[RRD-251; S-(2,4-Dichlorobenzyl)-isothiouronium chloride]** A cell-permeable and orally active isothiouronium compound that potently and selectively disrupts the Rb/Raf-1 interaction (IC_{50} = 77 nM in cell-free binding assays), while exhibiting no effect against Rb/B-Raf, Rb/E2F1, Rb/prohibitin, Rb/cyclin E, Rb/HDAC1, Raf-1/MEK1, or Raf-1/MEK2 interaction. Suppresses cellular E2F transcription activity and reduces serum-induced Rb phosphorylation. Shown to display Rb-dependent antitumor activity both in cultures *in vitro* and in mice *in vivo*.	25 mg
ZM 336372	**692000**	**{N-[5-(3-Dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide}** A potent, cell-permeable, reversible, ATP-competitive and specific inhibitor of the protein kinase c-Raf (IC_{50} = 70 nM). Inhibits c-Raf with ten-fold increased potency compared to B-Raf, but does not inhibit many other protein kinases (even at 50 µM) with the exception of SAPK2a/p38α (IC_{50} = 2 µM) and SAPK2b/p38ß2 (IC_{50} = 2 µM). The inhibition of c-Raf by ZM 336372 is competitive with respect to ATP.	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. Higher ROCK activity has been associated with endothelial cell dysfunction, cerebral ischemia, coronary vasospasms, and metabolic syndrome. Hence, ROCK inhibitors are gaining importance as therapeutic tools. 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**	**[Fasudil; (5-Isoquinolinesulfonyl)homopiperazine, 2HCl]** A cell-permeable, reversible, and ATP-competitive Ca^{2+} antagonist with anti-vasospastic properties. Inhibits protein kinase A (K_i = 1.6 µM), protein kinase G (K_i = 1.6 µM), and myosin light chain kinase (K_i = 36 µM). Also reported to potently inhibit Rho-associated kinase (ROCK; IC_{50} = 10.7 µM). Prevents apoptosis and enhances the survival and cloning efficiency of dissociated hES cells without affecting their pluripotency.	1 mg
Hydroxyfasudil	**390602**	**[1-(1-Hydroxy-5-isoquinolinesulfonyl)homopiperazine, HCl; HA1100]** A cell-permeable, hydroxylated metabolite of HA 1077 (Fasudil; Cat. No. 371970) that displays anti-anginal properties. Acts as an ATP-competitive and a reversible inhibitor of Rho-kinase (IC_{50} = 0.9 and 1.8 µM using a peptide and MLC as substrate, respectively) with ~100-fold greater selectivity over MLCK, MRCKß, and PKC. Reported to inhibit the Rho kinase-mediated contraction both *in vitro* and *in vivo*.	2 mg
Rho Kinase Inhibitor IV	**555554**	**H-1152, Glycyl (S)-(+)-2-Methyl-4-glycyl-1-(4-methylisoquinolinyl-5-sulfonyl)homopiperazine, 2HCl** A cell-permeable, reversible, and ATP-comptetive glycyl analog of Rho-Kinase Inhibitor (Cat. No. 555550) that inhibits ROCK with an improved selectivity (IC_{50} = 11.8 nM, > 10 µM, > 10 µM, 3.26 µM, 2.35 µM, and 2.57 µM for ROCKII, PKA, PKC, PKG, Aurora A, and CaMKII, respectively).	1 mg
Rho Kinase Inhibitor V	**555555**	**{N-(4-(1H-pyrazol-4-yl)phenyl)-2,3-dihydrobenzo[b][1,4]dioxine-2-carboxamide}** A cell-permeable pyrazolyl carboxamide compound that acts as a potent, ATP-binding pocket-targeting inhibitor of ROCK-II (IC_{50} = 1.5 nM) and effectively inhibits the myosin light chain 2 phosphorylation on Thr18/Ser19 in A7r5 cells (IC_{50} = 72 nM). It afftects the activities of PKA, MRCK, Akt1 (IC_{50} = 0.186, 1.19, and 1.41 µM, respectively) and CYP-450 enzymes (% inhibition of 2C9/2D6/3A4/1A2 at 10 µM = 87/40/1/20, respectively) only at much higher concentrations.	5 mg
Rho-Kinase Inhibitor	**555550**	**{H-1152; H-1152P; (S)-(+)-2-Methyl-1-[(4-methyl-5-isoquinolinyl) sulfonyl] homopiperazine, 2HCl; ROCK Inhibitor}** A cell-permeable isoquinolinesulfonamide compound that acts as a highly specific, reversible, potent, and ATP-competitive inhibitor of G-protein Rho-associated kinase (ROCK; K_i = 1.6 nM). Exhibits a much weaker affinity for other serine/threonine kinases (K_i = 630 nM for PKA, 9.27 µM for PKC, and 10.1 µM for MLCK). Shown to selectively block lysophosphatidic acid-induced, but not PDBu-induced, phosphorylation of myristoylated alanine-rich C kinase substrate MARCKS (IC_{50} = 2.5 µM) in NT-2 cells. Reported to be more potent and selective than Y-27632 (Cat. Nos. 688000 and 688001). A 10 mM (500 µg/128 µl) solution of Rho Kinase Inhibitor (Cat. No.555552) in H_2O is also available.	1 mg
InSolution™Rho-Kinase Inhibitor	**555552**	A 10 mM (500 µg/128 µl) solution of Rho Kinase Inhibitor (Cat. No. 555550) in H_2O.	500 µg
Rho-Kinase Inhibitor II	**555551**	**[N-(4-Pyridyl)-N'-(2,4,6-trichlorophenyl)urea]** A pyridyl urea compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of Rho-associated protein kinase (ROCK; IC_{50} = 0.2 µM). Displays little activity towards Erk, PKA, PKC, PDGFR, or c-Kit/SCFR (IC_{50} > 10 µM).	5 mg
Rho-Kinase Inhibitor III, Rockout	**555553**	**[3-(4-Pyridyl)-1H-indole]** A cell-permeable indolopyridine compound that acts as a selective, reversible, and ATP-competitive inhibitor of Rho kinase activity with an IC_{50} of 25 µM. Does not inhibit the activation of Rho kinase nor does it affect the *in vitro* activities of MLCK, PKCα, and SAPK2a/p38α. Shown to be 5-fold less potent than Y-27632 (Cat. No. 688000; IC_{50} = ~5 µM), and display a similar specificity profile as H-89 (Cat. No. 371963). Affects cell migration, inhibits blebbing (IC_{50} = ~ 12 µM in M2 cells), and decreases stress fibers in Bulb 3T3 cells at 50 µM.	10 mg
Rho/SRF Pathway Inhibitor, CCG-1423	**555558**	**N-(2-(4-Chloroanilino)-1-methyl-2-oxoethoxy)-3,5-bis(trifluoromethyl)benzamide** A cell-permeable benzamide compound that acts as an effective inhibitor against RhoA- and RhoC-mediated cellular activities by targeting signaling events downstream of $G\alpha_{12/13}$ and RhoA/C, affecting MKL recruitment and/or postrecruitment function of MKL1, but not SRF-SRE interaction or ROCK kinase activity. CCG-1423 is shown to inhibit RhoC-dependent cell growth in A375M2 and SK-Mel-147 (IC_{50} ≤300 nM) and block RhoC/ $G\alpha_{12}$-mediated PC-13 invasion in Matrigel assays (by ~90% at 3 µM).	25 mg

Rho Kinase (ROCK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Y-27632	**688000**	**[(R)-(+)-*trans*-N-(4-Pyridyl)-4-(1-aminoethyl)-cyclohexanecarboxamide, 2HCl; ROCK Inhibitor]** A highly potent, cell-permeable, reversible, and selective inhibitor of Rho-associated protein kinases (K_i = 140 nM for $p160^{ROCK}$). Also inhibits ROCK-II with equal potency. The inhibition is competitive with respect to ATP. Exhibits 10- to 50-fold lower affinity for PKC than $p160^{ROCK}$. Does not affect the activity of p21-activated protein kinase (PAK) even at higher concentrations (~100 µM). Also acts as a potent inhibitor of agonist-induced Ca^{2+} sensitization of myosin phosphorylation and smooth muscle contraction. Prevents apoptosis and enhances the survival and cloning efficiency of dissociated hES cells without affecting their pluripotency. A 5 mM (500 µg/296 µl) solution of Y-27632 (Cat. No.688001) in H_2O is also available.	1 mg 5 mg
InSolution™Y-27632	**688001**	A 5 mM (500 µg/296 µl) solution of Y-27632 (Cat. No. 688000) in H_2O.	500 µg

RNA-Dependent Protein Kinase Inhibitors

Product	Cat. No.	Comments	Size
PKR Inhibitor	**527450**	**RNA-Dependent Protein Kinase Inhibitor** An imidazolo-oxindole compound that acts as a potent, ATP-binding site directed inhibitor of PKR. Shown to effectively inhibit RNA-induced PKR autophosphorylation (IC_{50} = 210 nM) and rescue PKR-dependent translation block (IC_{50} = 100 nM). Inactive control is also available (Cat. No.527455).	5 mg
PKR Inhibitor, Negative Control	**527455**	**5-Chloro-3-(3,5-dichloro-4-hydroxybenzylidene)-1,3-dihydro-indol-2-one** An oxindole compound that serves as a negative control for PKR Inhibitor (Cat. No.527450). Shown to be inactive in inhibiting RNA-induced PKR autophosphorylation (IC_{50} > 100 µM) or in rescuing PKR-dependent translation block.	10 mg

TGF-ß Signaling Inhibitors

Transforming growth factor-ß (TGF-ß), a member of the TGF superfamily of proteins that includes activins, inhibins, and bone morphogenetic proteins (BMPs), regulates a wide array of cellular processes including cell differentiation, cellular senescence, immune response, wound healing, and apoptosis. TGF-ß signaling promotes growth and development during early embryogenesis. However, in mature tissues many cells respond to TGF-ß with either a cytostatic or apoptotic response. TGF-ß signaling involves its binding to the TGF-ß receptor type II (TGF-ßRII), which allows it to recruit TGF-ß receptor type I (TGF-ß RI) and assemble it as a heterodimeric receptor complex. TGF-ßRII phosphorylates TGF-ßRI in the glycine-serine rich region (GS sequence) and activates the serine/threonine kinase activity of TGF-ßRI, which in turn phosphorylates receptor-linked Smad (Small mothers against decapentaplegic) proteins. To prevent any spontaneous phosphorylation of Smads, the inhibitor molecule FKBP12 binds to the GS region of the TGF-ßRI and blocks the access of TGF-ßRII to this domain. This inhibitory effect is removed upon TGF-ß binding to the receptor. The TGF-ß receptor complex is internalized by lipid-raft and clathrin endocytotic pathways. The clathrin endocytotic pathway is considered to be essential for activation of the TGF-ß signaling cascade. The lipid-raft pathway for TGF-ß receptor internalization negatively regulates TGF-ß signaling by inducing receptor complex degradation.

The activated TGF-ßRI in the internalized complex phosphorylates specific Smad proteins. At least nine different Smad proteins have been reported in vertebrates that are classified as: (a) receptor-activated Smads (R-Smads): Smad1, Smad2, Smad3, Smad5, and Smad8; (b) co-mediator Smads: Smad4 and Smad10; and (c) inhibitory Smads (I-Smads): Smad6 and Smad7. R-Smads2 and 3 are involved in TGF-ß and activin signaling, whereas R-Smads 1, 5, and 8 are mediators of BMP signaling. Smad2 and Smad3 are directly phosphorylated by TGF-ßRI, which changes their conformation and releases these R-Smads from the receptor complex. The C-terminal phosphoserines of R-Smads are recognized by the Mad Homology 2 (MH2) domain of Smad4 that enables them to form a heterodimeric complex (R-Smad/Co-Smad). This complex then translocates to the nucleus where Smad proteins bind to their cognate DNA binding sites with low affinity. This binding is further enhanced in the presence of transcriptional co-activators. Both Smad3 and Smad4 bind to DNA sequences known as the Smad-binding elements (SBE); however, Smad2 participates in DNA-bound complexes via its interaction with Smad4. Genes for cyclin-dependent kinase inhibitors, p21 and p15, which mediate growth inhibitory processes, are up-regulated by TGF-ß stimulation. TGF-ß-induced growth inhibition is also achieved by down-regulation of c-Myc, which further amplifies the expression of p21 and p15.

Apart from its role as a growth inhibitor and tumor suppressor, TGF-ß also promotes tumor metastasis during late stages of tumor development. TGF-ß also modulates cell invasion, immune regulation, and microenvironment modification that cancer cells exploit to their advantage. Dysregulated TGF-ß signaling has been implicated in the pathogenesis of human solid tumors. Any disruption in TGF-ß signaling, either by mutational inactivation or by down regulation of expression of any of the signaling components involved, can lead to tumor development.

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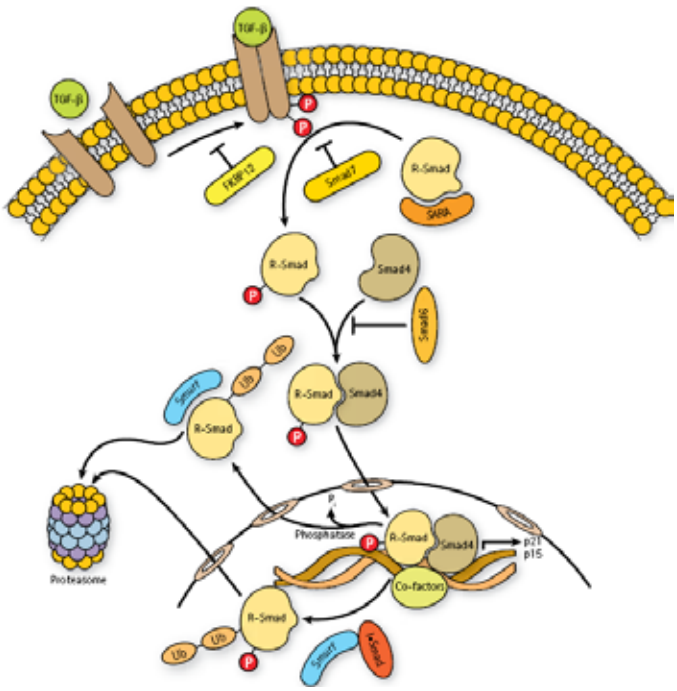

TGF-ß Receptor Kinase Inhibitors

Product	Cat. No.	Comments	Size
Smad3 Inhibitor, SIS3	**566405**	**{SIS3; 6,7-Dimethoxy-2-((2E)-3-(1-methyl-2-phenyl-1H-pyrrolo[2,3-b] pyridin-3-yl-prop-2-enoyl))-1,2,3,4-tetrahydroisoquinoline}** A cell-permeable pyrrolopyridine compound that selectively inhibits TGF-ß1-dependent Smad3 phosphorylation and Smad3-mediated cellular signaling with no effect on Smad2, p38 MAPK, ERK, or PI 3-K signaling.	1 mg
TGF-ß RI Inhibitor V	**616456**	**[SD-208; Transforming Growth Factor-ß Type I Receptor Kinase Inhibitor V; 2-(5-Chloro-2-fluorophenyl)pteridin-4-yl)pyridin-4-yl amine]** A cell-permeable pteridine compound that blocks TGF-ß signaling and displays anti-tumor properties. Acts as a potent, selective, and reversible inhibitor of TGF-ß RI/ALK5 kinase (EC_{50} = 48 nM). It inhibits p38α, MAPKAP, PKD, and p38α only at much higher concentrations (≥867 nM), while exhibiting little activity aginst TGF-ß RII, p38γ, JNK, ERK2, MAPKK6, PKA, or PKC even at concentrations as high as 50 µM. Inhibits TGF-ß-mediated cellular functions both *in vitro* and *in vivo*.	2 mg
TGF-ß RI Kinase Inhibitor	**616451**	**{ALK5 Inhibitor I; [3-(Pyridin-2-yl)-4-(4-quinonyl)]-1H-pyrazole; TßR-I Inhibitor; Transforming Growth Factor-ß Type I Receptor Kinase Inhibitor}** A cell-permeable diheteroaryl-substituted pyrazole compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of TGF-ß Receptor I kinase (IC_{50} = 51 nM). Displays ~15-fold greater selectivity over p38α MAP kinase (IC_{50} = 740 nM). Shown to inhibit TGF-ß-dependent cellular growth (IC_{50} = 89 nM in NIH 3T3 mouse fibroblasts) and transcription activation (IC_{50} = 47 nM in mink lung cells).	5 mg
TGF-ß RI Kinase Inhibitor II	**616452**	**[ALK5 Inhibitor II; 2-(3-(6-Methylpyridin-2-yl)-1H-pyrazol-4-yl)-1,5-naphthyridine; Transforming Growth Factor-ß Type I Receptor Kinase Inhibitor II]** A cell-permeable naphthyridinyl pyrazolo compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of TGF-ß type I receptor (ALK5; IC_{50} = 23 nM, 4 nM and 18 nM for ALK5 binding, ALK5 auto-phosphorylation and TGF-ß cellular assay in HepG2 cells, respectively). Minimally affects a panel of 9 closely related kinases including p38 MAPK at IC_{50} > 16 µM.	1 mg
TGF-ß RI Kinase Inhibitor III	**616453**	**{Transforming Growth Factor-b Type I Receptor Kinase Inhibitor III; 2-(5-Benzo[1,3]dioxol-4-yl-2-tert-butyl-1H-imidazol-4-yl)-6-methylpyridine, HCl}** A cell-permeable imidazolyl-pyridine compound that acts as a potent, ATP-competitive, reversible, and selective inhibitor of activin receptor-like kinase 4 (IC_{50} = 129 nM), 5 (IC_{50} = 47 nM), and 7. It inhibits p38 MAPKα only at much higher concentrations (IC_{50} = 10.6 µM) and has little effect against ALK1/2/3/6 as well as a panel of 26 other kinases.	2 mg
TGF-ß RI Kinase Inhibitor IV	**616454**	**[Kinase Inhibitor IV; Transforming Growth Factor-ß Type I Receptor; A-83-01; 3-(6-Methylpyridin-2-yl)-4-(4-quinolyl)-1-phenylthiocarbamoyl-1H-pyrazole]** A cell-permeable trisubstituted pyrazole compound that has been shown to selectively inhibit ALK-4/5/7-mediated (IC_{50} = 45, 12, and 7.5 nM, respectively, in luciferase transcription activity assays), but not ALK-1/2/3/6-mediated cellular signaling in Mv1Lu R4-2 transfectants expressing the individual Type I TGF-ß receptors. Inhibits TGF-ß-induced Smad2-phosphorylation in HaCaT cells and epithelial-to-mesenchymal transition in NMuMG cells at a concentration of 1 µM.	2 mg
TGF-ß RI Kinase Inhibitor VII	**616458**	**[ALK5 Inhibitor VII; 1-(2-((6,7-Dimethoxy-4-quinolyl) oxy)-(4,5-dimethylphenyl)-1-ethanone]** A cell-permeable quinoline compound that acts a potent ATP-competitive inhibitor of ALK5/TGF-ß Receptor I kinase activity (IC_{50} = 0.63 µM), while inhibiting c-Src only at higher concentrations (IC_{50} = 13 µM). Shown to block TGF-ß-induced Smad2 phosphorylation and Smad2/3 transcription activity (IC_{50} = 0.5 and 0.37 µM, respectively) in human lung cancer epithelial cell line A549.	5 mg
TGF-ß RI Kinase Inhibitor VIII	**616459**	**ALK5 Inhibitor VIII, SB-525334, 6-(2-tert-Butyl-5-(6-methyl-pyridin-2-yl)-1H-imidazol-4-yl)-quinoxaline** A cell-permeable quinoxaline compound that acts as a potent, highly selective, ATP-competitive inhibitor against type I TGF-ß receptor TßR-I/ALK5 (IC_{50} = 14.3 nM), while exhibiting 4-fold less potency toward ALK4 (IC_{50} = 58.5 nM) and little or no activity against ALK2/3/6 and a panel of 26 other commonly studied kinases (≤29% inhibition at 10 µM). Effectively blocks (by >95%) TGF-ß1-induced Smad2/3 activation (2 µM in ELT-3 cultures) and nuclear localization (1 µM in RPTE cultures), as well as TGF-ß1-dependent p3TP- and ARE-luciferase transcription (0.1 µM in HaCat cultures). SB-525334 is orally available and is shown to attenuate Bleomycin- and Puromycin-induced tissue fibrosis in mice and rats *in vivo*.	2 mg

Cell Adhesion Inhibitors

Cell adhesion molecules are multifunctional proteins involved in a number of regulatory processes, including cell growth, differentiation, proliferation, migration, and regeneration. Cell adhesion is crucial in the formation and main-tenance 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). During adhesion, cells form structures compromising of transmembrane and intracellular protein clusters giving rise to focal adhesions. A wide variety of adhesion molecules have been identified that fall into four major categories: cadherins, immunoglobulin (Ig)-like adhesion molecules, integrins, and selectins. Cell adhesion proteins are often transmembrane receptors that have domains extending into both the extracellular space and the intracellular space.

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 domain 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: 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 (FAK), 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
BAY 11-7082	**196870**	**{(E)3-[(4-Methylphenyl)sulfonyl]-2-propenenitrile}** Potential anti-inflammatory agent that selectively and irreversibly inhibits the TNF-α-inducible phosphorylation of IκBα (IC_{50} = 10 µM), resulting in a decreased expression of NF-κB and of adhesion molecules. Does not affect constitutive IκBα autophosphorylation. Inhibits TNF-α-induced surface expression of the endothelial-leukocyte cell adhesion molecules E-selectin, VCAM-1, and ICAM-1. A 100 mM (10 mg/483 µl) solution of BAY 11-7082 (Cat. No.196871) in DMSO is also available is also available.	10 mg
BAY 11-7085	**196872**	**{(E)3-[(4-*t*-Butylphenyl)sulfonyl]-2-propenenitrile}** Has biological properties very similar to those of BAY 11-7082 (Cat. No.196870). In addition, BAY 11-7085 shows potent anti-inflammatory properties *in vivo*.	10 mg
Cell Sheet Migration Inhibitor	**219469**	**{(4S)-3-[(E)-But-2-enoyl]-4-benzyl-2-oxazolidinone; UIC-1005** A cell-permeable N-(crotonyl)oxazolidinone compound that acts as a potent inhibitor of Raf kinase inhibitor protein (RKIP)/Raf1 kinase interaction. Shown to block eukaryotic cell migration (IC_{50} = 14 µM for inhibition of wound closure in MDCK cell monolayers) and decrease formation of lamellipodial protrusions at the wound margin. Also inhibits early development in frog embryos and tissue dynamics in embryonic explants. Displays no antibacterial activity. May serve as a useful tool for studying RKIP-mediated signaling pathways. Although locostatin is an irreversible inhibitor of RKIP, its cellular effects are generally reversible due to new biosynthesis.	10 mg
Cell Sheet Migration Inhibitor, Negative Control	**219470**	**[(4S)-3-butyryl-4-benzyl-2-oxazolidinone; UIC-1017]** A cell-permeable N-(butyryl)oxazolidinone compound that serves as a negative control for the Cell Sheet Migration Inhibitor (Cat. No.219469). Displays little bioactivity during wound closure and cell proliferation studies ($IC_{50} \geq$ 500 µM for wound closure in MDCK cell monolayers).	5 mg
Cyclo(Arg-Gly-Asp-D-Phe-Val)	**182015**	**(RGDFV Peptide, Cyclic)** Potent inhibitor of cell adhesion. Inhibits tumor cell adhesion to laminin and vitronectin substrates. *In vivo* investigations in rats showed it to be useful in the amelioration of ischemic acute renal failure in rats. Also inhibits tubular obstruction by preventing cell-cell adhesion. Inhibits the redistribution of c-Src into focal adhesions, thereby leading to impaired MAP Kinase activation.	1 mg
Focal Adhesion Kinase Inhibitor II	**324878**	**6-((4-((3-(Methanesulfonyl)benzyl)amino)-5-trifluoromethylpyrimidin-2-yl)amino)-3,4-dihydro-1H-quinolin-2-one** A cell-permeable pyrimidinyldiamino compound that acts as a selective, ATP-competitive, and potent FAK inhibitor (IC_{50} = 4 nM). It inhibits CDK7/cycH/MAT1 and CDK1/cycB only at much higher concentrations (IC_{50} = 197 and 486 nM, respectively) and exhibits little or much reduced activity against 39 other commonly studied kinases (≤64% inhibition at 1 µM). PF-573,228 effectively inhibits cellular FAK Tyr^{397} phosphorylation in various human, rat, and canine cell lines (IC_{50} = ~30-500 nM during an 1 h incubation period) and concomitant blockage of Tyr^{31} phosphorylation of the FAK downstream substrate paxillin is also demonstrated in rat fibroblast REF52 cultures. A useful tool for studying FAK-mediated cellular functions.	5 mg
FR-1	**5231701**	**(CRGDSPASSC, Cyclic)** A cyclic peptide containing the cell binding domain Arg-Gly-Asp and the associated cell migration sequence Pro-Ala-Ser-Ser of fibronectin. A potent inhibitor of ADP-induced platelet aggregation (IC_{50} = 7.6 µM).	1 mg
H-Arg-Gly-Asp-Ser-OH	**3340002**	**(Fibronectin Inhibitor; RGDS)** Shown to inhibit fibronectin function by binding to platelet-binding sites and to induce apoptosis in osteoblasts.	25 mg
H-Gly-Arg-Ala-Asp-Ser-Pro-OH	**3340052**	**(GRADSP)** Inactive control peptide for other fibronectin inhibitors.	5 mg 25 mg
H-Gly-Arg-Gly-Asp-Ser-OH	**3340027**	**(GRGDS)** A cell binding protein domain. Competitively inhibits direct binding of fibroblasts to fibronectin. In mice has been shown to prevent bladder tumor cell implantation. Reported to inhibit the migration of vascular smooth muscle cells into fibrin gels.	25 mg
H-Gly-Arg-Gly-Asp-Ser-Pro-OH	**3340035**	**(GRGDSP)** Shown to inhibit fibronectin binding to platelet-binding sites.	5 mg 25 mg
H-Gly-Arg-Gly-Asp-Thr-Pro-OH	**3340055**	**(GRGDTP)** Inhibits binding of fibrinogen, fibronectin, vitronectin, and von Willebrand factor to platelets. Also inhibits cell attachment to collagen, fibronectin, and vitronectin. Resistant to carboxypeptidases.	5 mg 25 mg

Cell Adhesion Inhibitors *continued*

Product	Cat. No.	Comments	Size
P-Selectin Antagonist	**561308**	**(Galloyl-N-gaba-WVDV-OH)** An N-terminal gallic acid substituted pentapeptide (γ-aminobutyric-WVDV) that acts as a specific, high affinity 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), and reduce the interaction between P-selectin and its endogenous ligand P-selectin glycoprotein ligand-1 (PSGL-1; complete inhibition at 500 nM).	5 mg
Pentoxifylline	**516354**	**[3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione; PTX]** A non-selective phosphodiesterase inhibitor. Inhibits endotoxin-induced synthesis of tumor necrosis factor-α (TNF-α). PTX inhibits the adhesion of T cells to the $ß_1$ and $ß_2$ integrin ligands VCAM-1 and ICAM-1. Also prevents the down-regulation of microsomal cytochrome P450 caused by lipopolysaccharides.	500 mg

Cell Proliferation and Sheet Migration Inhibitors

Product	Cat. No.	Comments	Size
SMC Proliferation Inhibitor-2w	**573117**	**N-(3',4',5',-Trimethoxybenzoyl)-(3,4-dimethoxy)ethylanthranilate** A diaryl amide analog that exhibits about 15 fold greater selectivity in inhibiting the proliferation of human coronary artery smooth muscle cells (IC_{50} = 310 nM) over the endothelial cells (IC_{50} = 4.6 µM). Exhibits over 80-fold greater potency than Tranilast (Cat. No.616400).	5 mg

Checkpoint Kinase Inhibitors

Eukaryotes have evolved elaborate sensory networks to detect and repair DNA damage and prevent alterations in their genetic material. In response to DNA damage, eukaryotic cells arrest either in G1 or S phase, to prevent replication of damaged genes, or in G2 phase to avoid segregation of defective chromosomes. Checkpoint kinases, Chk1 and Chk2, participate in various DNA-damage responses, including cell-cycle checkpoints, genome maintenance, DNA repair, and apoptosis. They phosphorylate several key proteins involved in cell cycle and block their activity.

Chk1, an evolutionarily conserved protein kinase, is expressed in the S and G2 phases of cell cycle of proliferating cells. It is activated by phosphorylation on Ser^{317} and Ser^{345} in response to DNA damage. Once activated, Chk1 phosphorylates Ser^{123} of Cdc25A, which targets it for ubiquitin-mediated degradation. The phosphorylated Cdc25A cannot dephosphorylate and activate Cdk1 and Cdk2, resulting in an arrest of cell cycle in the G1, S, and G2 phases. Chk1 also phosphorylates Ser^{216} (14-3-3 binding site) on Cdc25C and prevents its activation in the G2 phase. Phosphorylated Cdc25C cannot dephosphorylate and activate Cdk1. Recent research indicates that Chk1 is an ideal chemosensitization target and its inhibition can sensitize tumors, particularly those with p53-deficiency, to various chemotherapeutic agents.

Chk2 is structurally different from Chk1, but they share overlapping substrate specificities. Chk2 is activated following exposure to infrared light or topotecan, whereas Chk1 is activated by agents that interfere with DNA replication. This observation has lead to the belief that Chk1 blocks cell-cycle progression when replication is inhibited, whereas Chk2 acts when there are double-strand breaks. Chk2 is activated by DNA-strand-breaking agents such as ionizing radiation and topoisomerase inhibitors through the ATM-dependent pathway. The role of Chk2 in checkpoints is not clearly understood. However, it is reported to phosphorylate Cdc25A and inhibit its activity. Chk2 also phosphorylates Ser^{20} at the amino-terminal activation domain of p53 and regulates levels of p53 in response to DNA double strand breaks. Phosphorylation of Ser^{20} is not the only important event for p53 response induced by UV light. Chk2 can also regulate p53 through targeting several other phosphorylation sites.

Many current cancer treatments, including certain classes of chemotherapeutics, induce cytotoxicity by damaging DNA. However, many cancers become resistant to these therapies. Thus, modulating DNA-damage responses

to selectively enhance the sensitivity of cancer cells to these therapies is highly desirable. Inhibitors of Chk1 and Chk2 have shown potential to enhance the efficacy of DNA-damaging cancer therapeutic agents by selectively increasing the sensitivity of tumor cells.

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Checkpoint Kinase Inhibitors

Product	Cat. No.	Comments	Size
Chk2 Inhibitor	**220485**	**{5-(2-Amino-5-oxo-1,5-dihydroimidazol-4-ylidine)-3,4,5,10-2H-azepino[3,4-b] indol-1-one, HCl}** A cell-permeable, ATP competitive, and reversible indoloazepine compound that displays anti-proliferative and anti-inflammatory properties. Acts as a potent inhibitor of Chk2 (IC_{50} = 8 nM) that targets the ATP binding pocket. Exhibits selectivity for Chk2 over MEK1, Chk1, CK1δ, PKCα, PKCßII and CK2 (IC_{50} = 89 nM, 237 nM, 1.352 µM, 2.539 µM, 3.381 µM, and > 10.0 µM, respectively). Blocks the production of IL-2 and TNF-α by preventing the transcriptional activation of NF-κB (IC_{50} = 3.55 µM for IL-2 production in PMA-stimulated Jurkat T cells; 8.16 µM for TNF-α production in LPS-stimulated THP-1 cells). Also reported to suppress the growth of leukemic T cells (GI_{50} = 1.73 µM).	500 µg
Chk2 Inhibitor II	**220486**	**[2-(4-(4-Chlorophenoxy)phenyl)-1H-benzimidazole-5-carboxamide]** A cell-permeable and reversible benzimidazolo compound that acts as a potent and ATP-competitive inhibitor of Chk2 with an IC_{50} of 15 nM and a K_i of 37 nM. Displays ~ 1,000-fold greater selectivity over Cdk1/B and CK1 (IC_{50} = 12 µM and 17 µM, respectively) and only weakly affects the activities of a panel of 31 kinases (+ and $CD8^+$ T-cells from γ-irradiation-induced apoptosis with an EC_{50} of 3 µM and 7.6 µM, respectively.	1 mg
Isogranulatimide	**371957**	**(IGR)** A cell-permeable alkaloid containing indole/maleimide/imidazole skeleton that acts as a potent, reversible and ATP-competitive inhibitor of Chk1 (IC_{50} = 100 nM) and GSK-3ß (IC_{50} = 500 nM). Inhibits G_2 DNA damage checkpoint-associated kinases, Chk2, Cdk1, and DNA-PK only at much higher concentrations (IC_{50} = 3 µM, 10 µM, and 10 µM, respectively). Only minimally affects the activities of a panel of 11 other kinases tested ($IC_{50} \geq$ 40 µM). When used in combination with γ-irradiation, it is also reported to selectively arrest the growth of MCF-7 cells lacking p53 function.	1 mg
SB 218078	**559402**	**[9,10,11,12,-Tetrahydro-9,12-epoxy-1*H*-diindolo(1,2,3-fg:3',2',1'-kl) pyrrolo (3,4-i)(1,6)benzodiazocine-1,3(2*H*)-dione]** A cell-permeable, ATP-competitive, and reversible indolocarbazole derivative that acts as a potent and selective inhibitor of checkpoint kinase (Chk1) *in vitro*. It inhibits Chk1 phosphorylation of cdc25C with an IC_{50} of 15 nM. However, SB-218078 is a much weaker inhibitor of Cdc2 (IC_{50} = 250 nM) and PKC (IC_{50} = 1 µM).	1 mg
Scytonemin, *Lyngbya* sp.	**565715**	**(SCY)** A cell-permeable, dimeric indolo-phenol kinase inhibitor that exhibits anti-proliferative and anti-inflammatory properties. Scytonemin inhibits *polo*-like kinase 1 (Plk1), PKCß1, PKCß2, Cdk1/B, Myt1, and Chk1 (IC_{50} = 2.0, 3.4, 2.7, 3.0, 1.2, and 1.4 µM, respectively) in a dose-dependent manner, exhibiting little activity towards PKA or Tie2 (IC_{50} > 10 µM). Effectively inhibits growth factor- or serum-induced proliferation of cell types implicated in inflammatory response (IC_{50} < 8 µM for HUVEC, NHLF, and Jurkat) without any cytotoxic effect on nonproliferating cells.	1 mg
Wee1 Inhibitor	**681640**	**{4-(2-Chlorophenyl)-9-hydroxypyrrolo[3,4-c]carbazole-1,3-(2H,6H)-dione}** A pyrrolocarbazole compound that acts as a potent, ATP-binding site-targeting inhibitor of Wee1 (IC_{50} = 11 nM) in an ATP-competitive manner and displays ~40-fold selectivity over the related checkpoint kinase Chk1 (IC_{50} = 440 nM).	1 mg
Wee1 Inhibitor II	**681641**	**{6-Butyl-4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-c]carbazole-1,3-(2H,6H)-dione}** A pyrrolocarbazole compound that acts as a potent, ATP-binding site-targeting inhibitor of Wee1 (IC_{50} = 59 nM) with a ~590-fold selectivity over the related checkpoint kinase Chk1 (IC_{50} = 35 µM).	1 mg
Wee1/Chk1 Inhibitor	**681637**	**{4-(2-Phenyl)-9-hydroxypyrrolo[3,4-c]carbazole-1,3-(2H,6H)-dione}** A pyrrolocarbazole compound that acts as a potent and ATP-competitive inhibitor of checkpoint kinases Wee1 and Chk1 (IC_{50} = 97 nM and 47 nM, respectively). Inhibits PKC, Cdk4, or other CDKs only at much higher concentrations (IC_{50} = 3.4 µM, 3.75 µM, and >5 µM, respectively) and exhibits little effect against FGFR, PDGFR, or c-Src (IC_{50} >50 µM).	1 mg

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. Eleven members of the Cdk family are reported so far, and each member of the family has a specific function in cell-cycle. 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 S phase. Cdk2/cyclin A complex appears during 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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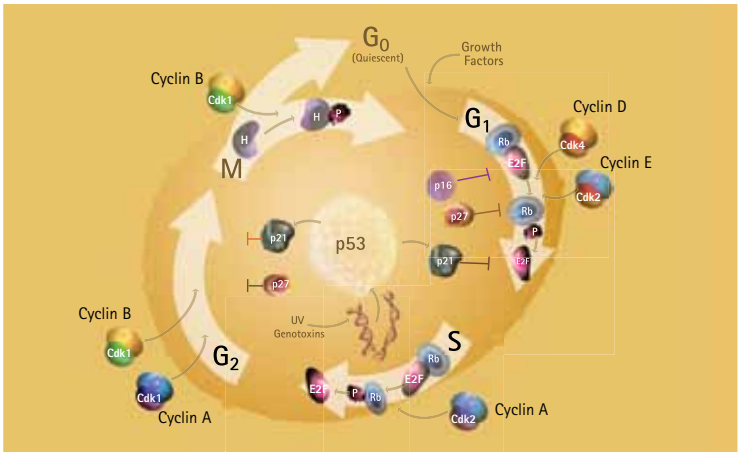

SELECTED CDK INHIBITORS (IC_{50} IN µM)

Product	Cat. No.	Cdk1	Cdk2	Cdk4	Cdk5
Alsterpaullone	126870	0.035	–	–	–
Alsterpaullone, 2-Cyanoethyl	126871	0.000230		–	0.030
Aloisine A	128125	0.15 (B)	0.12 (A), 0.40 (E)		0.20 (p25), 0.16 (p35)
Aloisine A, RP106	128135	0.70 (B)			1.50 (p35)
Aminopurvalanol A	164640	0.033	0.033 (A), 0.028 (E)		0.020 (p35)
Bohemine	203600	1.0	0.80 (E)	–	–
Cdk Inhibitor, p35	219457	0.10	0.80 (E)	–	–
Cdk1 Inhibitor	217695	5.8	–	–	25.0
Cdk1 Inhibitor, CGP74514A	217696	0.025 (B)	–	–	–
Cdk1 Inhibitor III	217697	28.8 (B)	–	–	–
Cdk1/2 Inhibitor II, NU6102	217713	0.0095 (B)	0.0054 (A3)	1.6 (D1)	–
Cdk1/5 Inhibitor	217720	0.60 (B)	–	–	0.40 (p25)
Cdk2 Inhibitor I	219442	–	0.038[a]	–	–
Cdk2 Inhibitor II	219445	0.78	0.060	–	–
Cdk2 Inhibitor III	238803	4.2 (B)	0.5 (A and E)	215.0 (D1)	–
Cdk2/5 Inhibitor	219448	–	2.0[b]	–	2.0[b]
Cdk4 Inhibitor	219476	2.1 (B)	0.52 (E)	0.076 (D1)	–
Fascaplysin, Synthetic	341251	> 100	> 50 (A and E)	0.35 (D1)	20.0
Indirubin-3'-monoxime	402085	0.18	-	-	0.10
Indirubin-3'-monoxime, 5-Iodo-	402086	0.025	-	-	0.020
Indirubin-3'-monoxime-5-sulphonic Acid	402088	0.005	-	-	0.007
Kenpaullone	422000	0.40 (B)	0.68 (A), 7.5 (E)	-	0.85
Olomoucine	495620	7.0 (B)	7.0 (A and E)	>1000 (D)	3.0 (p35)
Olomoucine II	495621	0.02 (B)			
Olomoucine, Iso	495622	> 500 (B)		> 1000 (D)	> 1000 (p35)
Oxindole I	499600	10.2	10.0 (E)	4.90	
Protein Kinase inhibitor, DMAP	476493	300 (B)			
Purvalanol A	540500	0.004 (B)	0.07 (A), 0.035 (E)		0.075 (p35)
Roscovitine	557360	0.65	0.7 (A and E)	>1000	0.2 (p35)
Roscovitine, (S)-Isomer	557362	0.80 (B)			
Staurosporine	569397	0.009	0.007	-	-
SU9516	572650	0.04 (B)	0.022 (A)	0.20 (D1)	
WHI-P180, Hydrochloride	681500		1.0		

Key: a = K_d; b = K_i. Letters in parentheses refer to associated cyclins or Cdks.

Cyclin-Dependent Kinase (Cdk) Inhibitors

Product	Cat. No.	Comments	Size
Aloisine A	**128125**	**{7-*n*-Butyl-6-(4-hydroxyphenyl)[5H]pyrrolo[2,3-b]pyrazine; RP107}** A cell-permeable pyrrolo-pyrazine compound that exerts anti-proliferative effects. Acts as a potent, selective, reversible, and ATP-competitive inhibitor of cyclin-dependent kinases (Cdks; IC_{50} = 150 nM, 120 nM, 400 nM, and 200 nM for Cdk1/cyclin B, Cdk2/cyclin A, Cdk2/cyclin E, and Cdk5/p25, respectively), glycogen synthase kinase-3 (GSK-3; IC_{50} = 500 nM and 1.5 µM for GSK-3α, GSK-3ß, respectively), and c-Jun N-terminal kinase (JNK; IC_{50} = ~ 3 - 10 µM). It inhibits several other enzymes (CK1, CK2, MAPKK, PKA, PKG, PKCs, and c-raf) poorly ($IC_{50} \geq$ 100 µM). Shown to arrest cells in both G_1 and G_2 phases (IC_{50} = 7 µM and 10.5 µM for undifferentiated human teratocarcinoma cells NT2 and differentiated postmitotic neurons hNT, respectively). Shown to selectively stimulate CFTR-dependent iodide efflux in wtCFTR-CHO, Calu-3 and F508del-CFTR-CF15 cells in the presence of 1 µM Forskolin (Cat. No.344270) with high affinity (EC_{50} = 150 nM, 140 nM and 111 nM, respectively).	5 mg
Aloisine, RP106	**128135**	**{7-*n*-Butyl-6-(4-methoxyphenyl)[5H]pyrrolo[2,3-b]pyrazine; RP106}** A cell-permeable pyrrolo-pyrazine compound that exerts anti-proliferative effects. Acts as a potent, selective, ATP-competitive inhibitor of CDK1/cyclin B, CDK5/p25, and GSK-3 (IC_{50} = 700 nM, 1.5 µM, and 920 nM, respectively).	5 mg
Alsterpaullone	**126870**	**{9-Nitro-7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one}** A cell-permeable, potent, reversible, and ATP competitive inhibitor of GSK-3ß (IC_{50} = 4 nM) and Cdk1/cyclin B (IC_{50} = 35 nM). Displays remarkable *in vitro* antitumor activity. Inhibits Tau phosphorylation at sites that are typically phosphorylated by GSK-3ß in Alzheimer's disease. Also inhibits Cdk5/p25-dependent phosphorylation of DARPP-32.	1 mg
Alsterpaullone, 2-Cyanoethyl	**126871**	A cell-permeable and reversible Alsterpaullone (Cat. No.126870) derivative that acts as a highly potent, ATP-competitive, selective inhibitor of Cdk1/cyclin B and GSK-3ß (IC_{50} = 230 pM and 800 pM, respectively; [ATP] = 15 µM). Displays ~37-fold greater selectivity for Cdk1/cyclin B over Cdk5/p25 (IC_{50} = 30 nM). Shown to inhibit other kinases in a commercially available testing screen panel ($pIC_{50} = -\log IC_{50}[M]$; pIC_{50} = ~ 7.5, 7.0, 7.0, 6.5, 6.5, 6.0, and 6.0 for Cdk2/A, Cdk4/D1, GSK-3ß, PDGFRß, Src, VEGFR-2, and VEGFR-3, respectively; [ATP] = 1 µM).	1 mg
Aminopurvalanol A	**164640**	**[(2R)-2-((6-((3-Amino-5-chlorophenyl)amino)-9-(1-methylethyl)-9H-purin-2-yl)amino)-3-methyl-1-butanol; NG-97]** A cell-permeable 2,6,9-trisubstituted purine analog that displays anti-mitotic as well as anti-tumor properties (GI_{50} = ~ 1.8 µM in the NCI 60-cell panel *in vitro* activity screen; potently inhibits the growth of KM12 colon cancer cells with a GI_{50} of 30 nM). Acts as a reversible and ATP-competitive inhibitor of Cdks (IC_{50} = 33 nM for Cdk1/cyclin B and Cdk2/cyclin A, 28 nM for Cdk2/cyclin E, and 20 nM for Cdk5/p35), and displays ~ 100-fold greater selectivity over a panel of kinases tested ($IC_{50} \geq$ 2.4 µM). Shown to induce cell differentiation by preferentially targeting the G_2/M-phase and act intracellularly by inhibiting both Cdks and MAPKs.	5 mg
Arcyriaflavin A, Synthetic	**181305**	**Arcyriaflavin A, Synthetic** This compound was originally isolated from the marine ascidian *Eudistoma* sp. Displays potent inhibitory activity against CDK4/D1 (IC_{50} = 59 nM). Also acts as a potent inhibitor of human cytomegalovirus (HCMV) replication in cell culture (IC_{50} = 200 nM).	1 mg
Bohemine	**203600**	**{[6-Benzylamino-2-(3-hydroxypropylamino)-9-isopropylpurine}** A synthetic, cell-permeable, cyclin-dependent kinase (CDK) inhibitor (IC_{50} = 1 µM) that is structurally similar to Olomoucine (Cat. No.495620) and Roscovitine (Cat. No.557360). Arrests cell cycle in the G_1/S boundary and activates *in vitro* matured bovine oocytes either alone or in combination with Ionomycin (Cat. Nos.407950 and407952).	1 mg 5 mg
Butyrolactone I	**203988**	A cell-permeable and highly selective inhibitor of cyclin-dependent protein kinases (Cdks) that inhibits cell cycle progression at the G_1/S and G_2/M transitions. Inhibits $p34^{cdk1}$/cyclinB (Cdk1; IC_{50} = 680 nM). Also selectively inhibits Cdk2 and Cdk5 kinases. Has little effect on casein kinase I, casein kinase II, EGF receptor kinase, MAP kinase, PKA, and PKC. Shown to prevent the phosphorylation of retinoblastoma protein and H1 histone. Also blocks Fas-induced apoptosis in HL-60 cells and shows antitumor effects on human lung cancer cell lines.	200 µg
Cdc2-Like Kinase Inhibitor, TG003	**219479**	**[Clk Inhibitor, TG003; (Z)-1-(3-Ethyl-5-methoxy-2,3-dihydrobenzothiazol- 2-ylidene)propan-2-one]** A cell-permeable dihydrobenzothiazolo compound that acts as a potent, specific, reversible, and ATP-competitive inhibitor of Clk-family of kinases (K_i = 10 nM for mClk1/Sty; IC_{50} = 15 nM, 20 nM, 200 nM, and > 10 µM for mClk4, mClk1, mClk2, and mClk3, respectively). Does not affect the activities of SRPK1, SRPK2, PKA, or PKC up to 1 µM. Shown to alter the regulation of alternative splicing mediated by phosphorylation of Ser/Arg-rich (SR) proteins both *in vitro* and *in vivo*. Suppresses early *Xenopus* developmental abnormality induced by excess levels of Clk-activity.	5 mg

Cyclin-Dependent Kinase (Cdk) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cdc7/9 Inhibitor	**217707**	**{PHA-767491; 2-(Pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridinone}** A cell-permeable pyrrolopyridinone compound that acts as a potent, reversible, and ATP-competitive inhibitor of Cdc7 and Cdk9 (IC_{50} = 10 and 34 nM, respectively) with good selectivity over a panel of 31 other kinases, including GSK-3ß, Cdk2, Cdk1, Cdk5, MK-2, Plk1, and Chk2 (IC_{50} = 0.22, 0.24, 0.25, 0.46, 0.47, 0.98, and 1.1 µM, respectively). Cellular treatment of PHA76749 results in a prevention of the activation of DNA replication origins without the inhibition of replication fork progression. Shown to inhibit the proliferation of 61 cell lines *in vitro* (IC_{50} ≤ 10 µM) and exhibit antitumor activity in both mice and rats *in vivo*.	5 mg
Cdk Inhibitor, p35	**219457**	**[2-(3-Hydroxypropylamino)-6-(*o*-hydroxybenzylamino)-9-isopropylpurine]** 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). Also displays anti-proliferative and pro-apoptotic effects. The correlation between inhibition of Cdk1/Cdk2 and inhibition of cell proliferation suggests that the anti-proliferative effects are due, in part, to Cdk inhibition.	1 mg
Cdk/CKI Inhibitor, (R)-DRF053	**219494**	**[2-(R)-(1-Ethyl-2-hydroxyethylamino)-6-(3-(2-pyridyl) phenylamino)-9-isopropylpurine, hydrate]** A cell-permeable ATP-binding pocket-targeting (R)-Roscovitine (Cat. Nos.550360 &t550364) derivative that is more potent than Roscovitine in inhibiting CDK1,CDK5, and CK1 activity (IC_{50} = 220,80,14 vs. 350, 200, 2300 nM, respectively), while maintaining selectivity against GSK-3α/ß (IC_{50} = 4.1 µM). The CDK/CK1 dual-specificity nature of (R)-DRF053 most likely accounts for its superior activity to that of (R)-Roscovitine against ß40 production from APP-expressing N2A cells (90% vs. 50% inhibition wtih 100 µM respective compound).	5 mg
Cdk/Crk Inhibitor	**219491**	**{RGB-286147; 1-(2,6-Dichlorophenyl)-1,5-dihydro-6-((4-(2-hydroxyethoxy) phenyl)methyl)-3-(1-methylethyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one}** A cell-permeable pyrazolo-pyrimidinone compound that acts as a potent, selective, and ATP-competitive inhibitor of Cdks (IC_{50} = 48 nM, 15 nM, 9 nM, 10 nM, 71 nM, and 9 nM for Cdk1/B, Cdk2/E, Cdk3/E, Cdk5/p35, Cdk7/H/MAT1, and Cdk9, respectively). It inhibits Cdk4/D1, Cdk6/D3, and GSK-3ß only at much higher concentrations (IC_{50} = 839 nM, 282 nM, and 754 nM, respectively) and exhibits little activity towards a panel of 60 other kinases. A broad-spectrum growth inhibitor toward tumor cells, but not non-transformed quiescent fibroblasts.	1 mg
Cdk/Cyclin Inhibitory Peptide III	**238807**	**(NBI1; Ac-RWIMYF-NH_2)** A protease-resistant, all D-amino acid hexapeptide that binds to a conserved region of cyclin A with high-affinity (K_d = ~ 102 nM) and disrupts the formation of Cdk/cyclin complex. Shown to inhibit the kinase activity of Cdk2/cyclin A, Cdk1/cyclin B1, and Cdk6/cyclin D3 (IC_{50} = 1.1, 2.0, and 6.4 µM, respectively) and affect the activities of GSK-3ß, MAPK2, Cdk2/cyclin E, and CKII only at much higher concentrations (IC_{50} = 10.4, 18.8, 51.4, and >200 µM, respectively). The cell-permeant derivative, TAT-NBI1, is also available (Cat. No.238808) respectively inhibits insulin signaling both in HepG2 cells *in vitro* and in *Drosophila* and mice *in vivo*.	5 mg
Cdk/Cyclin Inhibitory Peptide III, Cell-permeable	**238808**	**(TAT-NBI1; H-YGRKKRRQRRRG-RWIMYF-NH_2)** The cyclin A binding peptide NBI1(Cat. No.238807) is made cell-permeable with an N-terminal TAT sequence. Shown to induce cell cycle arrest and apoptosis in tumor cells.	2 mg
Cdk1 Inhibitor	**217695**	**[3-(2-Chloro-3-indolylmethylene)-1,3-dihydroindol-2-one]** A cell-permeable indolylmethylene-2-indolinone derivative that exhibits potent anti-proliferative properties (IC_{50} = 2 µM HeLa cells). Acts as a selective, reversible and ATP-competitive inhibitor of Cdk1/cyclin B (IC_{50} = 5.8 µM). Also inhibits Cdk5 with a IC_{50} = 25 µM. Binds to the ATP pocket on the Cdk1 active site. Does not affect the activity of GSK-3ß even at 100 µM concentrations.	5 mg
Cdk1 Inhibitor III	**217697**	**{Ethyl-(6-hydroxy-4-phenylbenzo[4,5]furo[2,3-b])pyridine-3-carboxylate}** A cell-permeable 1-aza-9-oxafluorene compound that acts as a highly selective Cdk1/cyclin B inhibitor (IC_{50} = 28.8 µM) with very little activity against Cdk5/p25, Cdk2/E, or Cdk4/D1. Unlike other Cdk inhibitors, it exhibits potent inhibitory effect against P-glycoprotein-mediated MDR (multidrug resistance) in cancer cells (~9-fold more potent than verapamil). Its special bifunctional cytostatic property makes it an excellent tool for research in cancer treatment.	1 mg 5 mg
Cdk1 Inhibitor IV, RO-3306	**217699**	A cell-permeable quinolinyl thiazolinone compound that acts as a potent and ATP-competitive inhibitor of Cdk1 (K_i = 35 nM and 110 nM for Cdk1/B1 and Cdk1/A, respectively). It affects Cdk2/E, PKCδ, and SGK only at much higher concentrations (K_i = 340, 318, and 497 nM, respectively), and shows little effect against Cdk4/D and six other commonly studied kinases (K_i ≥ 2 µM). Short-term treatment for up to 20 hrs results in fully reversible G2/M cell cycle arrest, while prolonged treament (>48 hrs) results in apoptotic cell death in proliferating cancer cells, but not in nontumorigenic epithelial cell lines.	5 mg

Cyclin-Dependent Kinase (Cdk) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cdk1 Inhibitor, CGP74514A	**217696**	**[N-(*cis*-2-Aminocyclohexyl)-N-(3-chlorophenyl)-9-ethyl-9H-purine-2,6-diamine; CGP74514A]** A cell-permeable and ATP competitive 2,6,9-substituted purine derivative that acts as a potent, selective inhibitor of Cdk1/cyclin B (IC_{50} = 25 nM). Reported to affect the activities of other kinases only at much higher concentrations (IC_{50} = 6.1 µM, 125 µM, and > 10 µM for PKCα, PKA, and EGFR, respectively). Shown to induce mitochondrial damage and apoptosis (≥ 3 µM) in several human leukemia cell lines. At lower concentrations (~1 µM), an initial G_2M cell cycle arrest was observed in U937 cells, which eventually lead to apoptosis.	5 mg
Cdk1/2 Inhibitor II, NU6102	**217713**	**[6-Cyclohexylmethoxy-2-(4'-sulfamoylanilino)purine]** A cell-permeable 2,6-disubstituted purine compound that displays antiproliferative properties. Acts as a potent and ATP-competitive inhibitor of Cdk1/cyclin B and Cdk2/cyclin A3 (IC_{50} = 9.5 nM and 5.4 nM). Displays greater selectivity for Cdk1/2 over other kinases tested (IC_{50} = 600 nM, 800 nM, 900 nM and 1.6 µM for ROCKII, PDK1, DYRK1A and Cdk4/D1, respectively). Shown to inhibit human MCF-7 breast carcinoma cell growth with a GI_{50} of 8 µM.	1 mg 5 mg
Cdk1/2 Inhibitor III	**217714**	A cell-permeable triazolo-diamine compound that displays anti-proliferative properties in various human cancer cells (IC_{50} = 20 nM, 35 nM and 92 nM in HCT-116, HeLa, and A375 cells, respectively). Acts as a highly potent, reversible, ATP-competitive inhibitor of Cdk1/cyclin B and Cdk2/cyclin A (IC_{50} = 600 pM and 500 pM, respectively) with selectivity over VEGF-R2 (IC_{50} = 32 nM), GSK-3ß (IC_{50} = 140 nM), and a panel of eight other kinases (IC_{50} ≥ 1 µM).	1 mg
Cdk1/5 Inhibitor	**217720**	**(3-Amino-1H-pyrazolo[3,4-b]quinoxaline)** A 3-amino substituted pyrazoloquinoxaline compound that acts as a selective inhibitor of cyclin-dependent kinases 1 and 5 (Cdks; IC_{50} = 0.6 µM and 0.4 µM for Cdk1/cyclin B and Cdk5/p25, respectively). Also shown to inhibit GSK-3ß with (IC_{50} = 1 µM). Does not inhibit Cdc25 phosphatase activity (IC_{50} > 10 µM).	5 mg
Cdk2 Inhibitor I	**219442**	**(YSFVHHGFFNFRVSWREMLA)** Inhibitor of the cyclin-dependent kinase Cdk2 (K_d = 38 nM).	1 mg
Cdk2 Inhibitor II	**219445**	**(Compound 3)** A cell-permeable, reversible, ATP-competitive, potent and selective inhibitor of Cdk2 (IC_{50} = 60 nM).	1 mg 5 mg
Cdk2 Inhibitor III	**238803**	**[2(*bis*-(Hydroxyethyl)amino)-6-(4-methoxybenzylamino)-9-isopropyl-purine]** A cell-permeable purine analog that acts as a potent, selective, reversible, and ATP-competitive inhibitor of Cdk2 (IC_{50} = 0.5 µM for Cdk2/A and Cdk2/E; 4.2 µM for Cdk1/B; 215 µM for Cdk4/D1). Inhibits other kinases only at much higher concentrations (IC_{50} > 1.25 mM for MAPK, PKA, and PKC). Shown to induce tumor cells growth arrest (IC_{50} = ~1.25-20 µM) *in vitro* and prevent neointima formation *in vivo*.	1 mg 5 mg
Cdk2 Inhibitor IV, NU6140	**238804**	A highly cell-permeable purine compound that displays anticancer properties and acts as a selective and ATP-competitive inhibitor of Cdks (IC_{50} = 6.6 µM, 0.41 µM, 5.5 µM, 15 µM and 3.9 µM for Cdk1/cyclin B, Cdk2/cyclin A, Cdk4/cyclin D, Cdk5/p25 and Cdk7/cyclin H, respectively). Shown to cause cell cycle arrest at the G_2/M phase and induce apoptosis by activating caspases and down-regulation survivin. Synergistically potentiates paclitaxel cytotoxicity and apoptotic response in HeLa and OAW42 cells.	5 mg
Cdk2/5 Inhibitor	**219448**	**[N4-(6-Aminopyrimidin-4-yl)-sulfanilamide, HCl; PNU 112455A]** An aminopyrimidine derivative that acts as a selective and ATP-competitive inhibitor of Cdk2/cyclin E and Cdk5/p25 (K_i = 2 µM). Binds to the ATP-binding pocket of Cdk2. Does not affect the activities of c-Met, IGF-1 receptor tyrosine kinase, cAMP-dependent kinase, and ERK2 at concentrations as high as 100 µM.	5 mg
Cdk2/9 Inhibitor	**238806**	**[(4-(2-Amino-4-methylthiazol-5-yl)pyrimidin-2-yl)-(3-nitrophenyl)amine]** A cell-permeable aminopyrimidinyl compound that acts as a potent and ATP-competitive inhibitor of Cdk2/E and Cdk9/T1 (K_i = 2 nM and 4 nM, respectively). It also inhibits GSK-3ß, Cdk4/D_1, Cdk7/H, Cdk1/B, and Abl at higher concentrations (K_i = 20, 53, 70, 80, and 160 nM, respectively), but exhibits little activity towards 9 other kinases (K_i > 1.0 µM). Shown to inhibit phosphorylation of cellular Cdk substrates, pRb and RNA polymerase II, and Cdk2-mediated S-phase transition.	5 mg
Cdk2/Cyclin Inhibitory Peptide I	**238801**	**(Tat-LFG; YGRKKRRQRRRGPVKRRLFG)** A cell-permeable peptide inhibitor derived from the consensus sequence of cyclin/Cdk2 binding motif, PVKRRLFG, that serves as the docking site for cyclin-dependent kinase-2 (Cdk2)/cyclin complexes. Blocks the phosphorylation of substrates by Cdk2/cyclin A and Cdk2/cyclin E complexes. The inhibitor is a chimeric peptide that contains the N-terminal residues from the HIV Tat protein which direct the uptake of the molecule across the cell membrane. Has been shown to preferentially induce apoptosis only in transformed cells and not in nontransformed cells.	500 µg

Cyclin-Dependent Kinase (Cdk) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cdk4 Inhibitor	**219476**	**{2-Bromo-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione}** A cell-permeable, unsymmetrical indolocarbazole compound that displays antiproliferative properties. Acts as a potent, selective, reversible and ATP-competitive inhibitor of Cdk4/D1 (IC_{50} = 76 nM). It inhibits the activity of other Cdk's only at much higher concentrations (IC_{50} = 520 nM and 2.1 µM for Cdk2/E and Cdk1/B, respectively) and shows little activity towards CaMKII, PKA, or GSK-3ß (IC_{50} ≥ 12.4 µM). Shown to inhibit tumor cells growth (IC_{50} < 3.0 µM in HCT-116 and NCI-H460 cells) by blocking Rb phosphorylation and inducing G1 cell cycle arrest.	1 mg
Cdk4 Inhibitor II, NSC 625987	**219477**	**[1,4-Dimethoxy-9-thio(10H)-acridone]** A thioacridone compound that acts as a reversible and potent substrate-competitive inhibitor of Cdk4/cyclin D1 (IC_{50} = 200 nM). Displays ~500-fold greater selectivity for Cdk4/cyclin D1 over Cdc2/cyclin A (Cdk1/cyclin A), Cdk2/cyclin A, and Cdk2/cyclin E (IC_{50} > 100 µM).	5 mg
Cdk4 Inhibitor III	**219478**	**[5-(N-(4-Methylphenyl)amino)-2-methyl-4,7-dioxobenzothiazole]** A cell-permeable dioxobenzothiazole compound that acts a selective Cdk4 inhibitor (IC_{50} = 6.0 µM for Cdk4/D1 and > 200 µM for Cdk2/A). Exhibit better cytotoxic potential against cancer cells (IC_{50} = 0.61, 1.08, 0.30, and 1.21 µg/ml against A 549, Col 1, HL-60, and HepG2 tumor cells, respectively) than Cisplatin (Cat. No.232120).	5 mg
Cdk4/6 Inhibitor IV	**219492**	**CINK4,** ***trans*****-4-((6-(ethylamino)-2-((1-(phenylmethyl)-1H-indol-5-yl)amino)-4-pyrimidinyl)amino)-cyclohexanol** A cell-permeable triaminopyrimidine compound that acts as a reversible and ATP-competitive inhibitor against Cyclin D1-complexed, but not Cyclin D2-complexed, Cdk4 and Cdk6 (IC_{50} = 1.5 and 5.6 µM, respectively) with much reduced activity against Cdk5/p35 (IC_{50} = 25 µM) and little or no activity towards Cdk1/CycB, Cdk2/CycA, Cdk2/CycE, v-abl, c-met, IGF-1R, or IR (IC_{50} >10 µM). CINK4 (at 5 and 10 µM) effectively inhibits cellular Cdk4 substrate pRb phosphorylation and prevents serum-stimulated G_1/S transition of serum starved pRb-positive, but not pRb-negative, cultures. CINK4 is shown to exert a ~46% suppression of human colon carcinoma HCT116-derived tumor growth in mice *in vivo* (30 mg/kg; twice a day, i.p.).	5 mg
Cdk9 Inhibitor II	**238811**	**[4-(3,5-Diamino-1H-pyrazol-4-ylazo)-phenol]** A cell-permeable azo-pyrazole compound that acts as a potent, ATP-competitive, and Cdk9-selective inhibitor (IC_{50} = 350 nM, using Cdk9/T1). It inhibits Cdk1/B, Cdk2/E, Cdk2/A, Cdk4/D1, Cdk7/H, and p70S6K only at much higher concentrations (IC_{50} = 44, 20, 69, 13.5, 26, and 10 µM, respectively) and shows little or no activity against eight other commonly studied kinases even at concentrations as high as 10 µM. Shown to exhibit antiproliferative activity in human tumor cell lines.	5 mg
Compound 52	**234503**	**[2-(2-Hydroxyethylamino)-6-(3-chloroanilino)-9-isopropylpurine]** A potent, cell-permeable, reversible, selective, and ATP-compatible inhibitor of the cell cycle-regulating kinase, Cdc28p (IC_{50} = 7 µM), and the related Pho85p kinase (IC_{50} = 2 µM).	1 mg
CR8, (R)-Isomer	**203881**	**[(R)-CR8; 2-(R)-(1-Ethyl-2-hydroxyethylamino)-6-(4-(2-pyridyl)benzyl)-9-isopropylpurine]** A cell-permeable (R)-DRF053 (Cat. No.219494) analog that acts as an ATP-binding pocket-targeting CDK/CK1 dual-specific inhibitor (IC_{50} = 0.09, 0.072, 0.041, 0.11, 1.10, 0.18, and 0.40 µM against CDK1/B, CDK2/A, CDK2/E, CDK5/p25, CDK7/H, CDK9/T, and CK1δ/, respectively). As is the case with (R)-DRF053, (R)-CR8 inhibits CDK/CK1 more effectively than (R)-Roscovitine (Cat. Nos.550360 &t550364), while maintaining similar selectivity profile over other types of kinases (IC_{50} = 3.6, 3.6, and 12.0 µM against Dyrk1A, Erk2, and GSK-3α/ß, respectively). Both the (R)-CR8 and (S)-enantiomer (Cat. No.203882) are much more effective than (R)-Roscovitine in apoptosis induction in cell cultures.	5 mg
CR8, (S)-Isomer	**203882**	**[(S)-CR8; 2-(S)-(1-Ethyl-2-hydroxyethylamino)-6-(4-(2-pyridyl)benzyl)-9-isopropylpurine]** A cell-permeable (R)-DRF053 (Cat. No.219494) analog that acts as an ATP-binding pocket-targeting CDK/CK1 dual-specific inhibitor (IC_{50} = 0.15, 0.080, 0.060, 0.12, 0.11, and 0.61 µM against CDK1/B, CDK2/A, CDK2/E, CDK5/p25, CDK9/T, and CK1δ/, respectively). Although (S)-CR8 displays in general similar kinase inhibitory profile as its (R)-enantiomer (Cat. No.203881), it does exhibit more enhanced and reduced activity against, respectively, Dyrk1A (IC_{50} = 0.9 µM) and GSK-3α/ß (IC_{50} ≥ 30 µM). Both (R)- and (S)-CR8 are much more effective than (R)-Roscovitine (Cat. Nos.550360 and550364) in apoptosis induction in cell cultures.	5 mg
Cyclin-Dependent Protein Kinase Inhibitor Set	**219428**	Contains 5 mg of Olomoucine (Cat. No.495620), 1 mg of Iso-Olomoucine (Cat. No.495622), and 1 mg of Roscovitine (Cat. No.557360). Supplied with an informational insert.	1 set

Cyclin-Dependent Kinase (Cdk) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Fascaplysin, Synthetic	**341251**	A cell-permeable red pigment, originally isolated from marine sponge, that acts as a potent, ATP-competitive inhibitor of Cdk4/D1 (IC_{50} = 0.35 µM). It inhibits Cdk6/D1 with much lower potency (IC_{50} = 3.4 µM) and has been shown not to affect the activities of several other Cdk's (IC_{50} > 20 µM) and tyrosine kinases (IC_{50} > 10 µM). Part of its biological effects may also be attributed to its ability to intercalate into DNA. Has also been shown to display anti-microbial activity.	1 mg
GSK-3 Inhibitor IX	**361550**	**BIO; (2'Z,3'E)-6-Bromoindirubin-3'-oxime** A cell-permeable bis-indolo (indirubin) compound that acts as a highly potent, selective, reversible, and ATP-competitive inhibitor of GSK-3α/ß (IC_{50} = 5 nM). Its specificity has been tested against various Cdk's (IC_{50} = 83, 300, 320, and 10,000 nM for Cdk5/p25, Cdk2/A, Cdk1/B, and Cdk4/D1, respectively) as well as many other commonly studied kinases (IC_{50} ≥ 10 µM), including MAP kinases, PKA, PKC isoforms, PKG, CK, and IRTK. Inhibition of GSK by BIO has been shown to result in the activation of Wnt-signaling pathway and sustained pluripotency in human and murine ESCs (embryonic stem cells). Reported to maintain self-renewal in human and mouse embryonic stem cells. Also induces the differentiation of neonatal cardiomyocytes. A 10 mM (500 µg/140 µl) solution of GSK-3 Inhibitor IX (Cat. No.361552) in DMSO is also available.	1 mg
InSolution™GSK-3 Inhibitor IX	**361552**	A 10 mM (500 µg/140 µl) solution of GSK-3 Inhibitor IX (Cat. No. 361550) in DMSO.	500 µg
Indirubin Derivative E804	**402081**	A cell-permeable indirubin derivative (IDR) that blocks the Src-Stat3 signaling pathway and displays anti-tumor properties. Shown to be a potent, reversible, and ATP-competitive inhibitor of the kinase activities of Src (IC_{50} = 430 nM), Cdk1/cyclin E (IC_{50} = 210 nM), Cdk2/cyclin A (IC_{50} = 540 nM), and Cdk1/cyclin B (IC_{50} = 1.65 µM). Reduces the tyrosine phosphorylation levels of Src, JAK1, and Stat3 in MDA-MB-468 cells in a time- and dose-dependent manner. Selectively induces apoptosis in cells expressing high levels of active Stat3, but not cells lacking activated Stat3. The apoptotic effect of E804 is shown to be due to the down-regulation of antiapoptotic proteins Mcl-1 and survivin.	1 mg
Indirubin-3'-monoxime, 5-Iodo-	**402086**	A highly potent cell-permeable and reversible inhibitor of glycogen synthase kinase-3ß (GSK-3ß; IC_{50} = 9 nM). Also inhibits Cdk1 (IC_{50} = 25 nM) and Cdk5 (IC_{50} = 20 nM) activities. Acts by binding to the ATP-binding pocket of these enzymes.	1 mg
Indirubin-3'-monoxime	**402085**	A potent, reversible, and ATP-compatible inhibitor of GSK-3ß (glycogen synthase kinase 3ß), Cdk1 (cyclin-dependent kinase1) and Cdk5 (IC_{50} = 22 nM, 180 nM, and 100 nM, respectively). Inhibits the proliferation of a large range of cells by arresting them in the G_2/M phase of the cell cycle. Inhibits Tau phosphorylation *in vitro* and *in vivo* at Alzheimer's disease-specific sites. Also reported to inhibit the *in vivo* phosphorylation of DARPP-32 by Cdk5 on Thr^{75}.	1 mg
Indirubin-3'-monoxime-5-sulphonic Acid	**402088**	A potent, reversible, and selective inhibitor of Cdk1 (IC_{50} = 5 nM) and Cdk5 (IC_{50} = 7 nM) and glycogen synthase kinase-3ß (GSK-3ß; IC_{50} = 80 nM). The inhibition is competitive with respect to ATP.	1 mg
Kenpaullone	**422000**	**{9-Bromo-7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one; NSC-664704}** A potent, cell-permeable, and reversible inhibitor of glycogen synthase kinase-3ß (IC_{50} = 230 nM), Lck (IC_{50} = 470 nM), and cyclin-dependent kinases (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). Also inhibits other kinases such as c-Src (IC_{50} = 15 µM), casein kinase II (IC_{50} = 20 µM), ERK1 (IC_{50} = 20 µM), and ERK2 (IC_{50} = 9 µM). Inhibition is competitive with respect to ATP binding.	1 mg
Olomoucine	**495620**	**[2-(2-Hydroxyethylamino)-6-benzylamino-9-methylpurine]** A purine derivative that acts as a potent, reversible and selective inhibitor of $p34^{cdk1}$/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 MAP kinase (IC_{50} = 25 µM). Acts by competing for the ATP binding domain of the kinase. Exhibits reduced sensitivity towards related kinases, $p34^{cdk4}$/cyclin D (IC_{50} > 1 mM), and $p40^{cdk6}$/cyclin D3 (IC_{50} > 250 µM). Does not significantly affect the activity of other protein kinases at 1 mM. Known to inhibit DNA synthesis in interleukin-2-stimulated T lymphocytes and trigger G_1 arrest similar to that observed in interleukin-2-deprived cells. Also used to synchronize cells in G_1. A 50 mM (5 mg/336 µl) solution of Olomoucine (Cat. No.495624) in DMSOis also available.	1 mg 5 mg
InSolution™Olomoucine	**495624**	A 50 mM (5 mg/336 µl) solution of Olomoucine (Cat. No. 495620) in DMSO.	5 mg

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Cyclin-Dependent Kinase (Cdk) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Olomoucine II	**495621**	**[6-(2-Hydroxybenzylamino)-2-((1R)-(hydroxymethyl) propyl)amino)-9-isopropylpurine]** A cell-permeable 2,6,9-trisubstituted purine analog that acts as a potent, reversible, and ATP-competitive inhibitor of Cdk1/B with an IC_{50} of 20 nM and displays increased potency over purvalanol A (Cat. No.540500; IC_{50} = 50 nM), Roscovitine (Cat. No.557360; IC_{50} = 450 nM), Bohemine (Cat. No.203600; IC_{50} = 1.1 µM) and Olomoucine (Cat. No.495620; IC_{50} = 7.0 µM). Further, exerts greater *in vitro* cytotoxicity in various cancer cell lines (IC_{50} = 3.0 µM, 5.3 µM, 6.3 µM, 6.3 µM and 11.1 µM for CEM, MCF7, HOS, G631 and K562, respectively).	5 mg
Olomoucine, Iso-	**495622**	**[6-Benzylamino-2-(2-hydroxyethylamino)-7-methylpurine; Iso-Olomoucine]** A structural isomer of Olomoucine (Cat. No.495620) that is used as a negative control in studies involving olomoucine (IC_{50} > 500 µM for $p34^{cdk1}$/cyclin B; IC_{50} > 1 mM for $p33^{cdk5}$/p35; IC_{50} > 1 mM for $p34^{cdk4}$/cyclin D).	1 mg 5 mg
Pfmrk Inhibitor, WR 216174	**528140**	**[5-Bromo-3-(2-(4-Fluorophenyl)-2-oxoethylidine)-1,3-dihydroindol-2-one]** A cell-permeable oxindole compound that acts as an ATP-competitive, reversible, and specific inhibitor of Pfmrk (IC_{50} = 1.4 µM), a Cdk from the malaria-causing parasite *Plasmodium falciparum*. Displays low activity against PfPK5 (IC_{50} = 190 µM) and human Cdk1/B (IC_{50} = 29 µM).	5 mg
Purvalanol A	**540500**	**[2-(1R-Isopropyl-2-hydroxyethylamino)-6-(3-chloroanilino)-9-isopropyl-purine]** A potent, cell-permeable, reversible, and selective inhibitor of cyclin-dependent kinases (Cdks; IC_{50} = 4 nM for Cdc2/cyclin B; IC_{50} = 70 nM for Cdk2/cyclin A; IC_{50} = 35 nM for Cdk2/cyclin E; and IC_{50} = 75 nM for Cdk5/p35).	1 mg
Roscovitine	**557360**	**[2-(R)-(1-Ethyl-2-hydroxyethylamino)-6-benzylamino-9-isopropylpurine]** A potent, reversible, and selective inhibitor of cyclin-dependent kinases (Cdks) that exhibits about ten-fold greater efficacy towards $p34^{cdk1}$ and $p33^{cdk2}$ and twenty-fold greater efficacy towards $p33^{cdk5}$ relative to Olomoucine (Cat. No.495620). Inhibits $p34^{cdk1}$/cyclin B (IC_{50} = 650 nM), $p33^{cdk2}$/cyclin A (IC_{50} = 700 nM), $p33^{cdk2}$/cyclin E (IC_{50} = 700 nM), and $p33^{cdk5}$/p35 (IC_{50} = 200 nM) by competing for the ATP binding domain of the kinases. Exhibits reduced sensitivity towards related kinases including ERK1 and ERK2 (IC_{50} = 34 µM and 14 µM, respectively). Roscovitine does not significantly affect the activity of other protein kinases even at 100 µM, including $p34^{cdk4}$/cyclin D1 and $p40^{cdk6}$/cyclin D2. Compared to olomoucine, roscovitine displays increased anti-mitotic activity at the G_1/S and G_2/M phases of the cell cycle. A 50 mM (5 mg/282 µl) solution of Roscovitine (Cat. No.557364) in DMSO is also available.	1 mg 5 mg
InSolution™Roscovitine	**557364**	A 50 mM (5 mg/282 µl) solution of Roscovitine (Cat. No. 557360) in DMSO.	5 mg
Roscovitine, (S)-Isomer	**557362**	**[2-(S)-(1-Ethyl-2-hydroxyethylamino)-6-benzylamino-9-isopropylpurine]** The (S)-enantiomer of the potent cyclin-dependent kinase (Cdk) inhibitor Roscovitine (Cat. No.557360). Potently inhibits $p34^{cdk1}$/cyclin B kinase (IC_{50} = 800 nM).	1 mg
SU9516	**572650**	**{3-[1-(3H-Imidazol-4-yl)-meth-(Z)-ylidene]-5-methoxy-1,3-dihydro-indol-2-one}** A cell-permeable 3-substituted indolinone compound that displays anti-proliferative and proapoptotic properties in tumor cells. Acts as a potent, selective, reversible, and ATP-competitive inhibitor of cyclin dependent kinases (Cdks; IC_{50} = 22 nM for Cdk2/A; 40 nM for Cdk1/B; 200 nM for Cdk4/D1). It shows no significant effect (IC_{50} >10 µM) on the activities of PKC, p38, PDGFRß, or EGFR. Inhibits the proliferation of growth factor-stimulated colon carcinoma cells by binding to Cdk2 and preventing the phosphorylation of pRb and its dissociation from E2F.	5 mg
UCN-01	**539644**	**(Staurosporine, 7ß-Hydroxy, *Streptomyces* sp; 7-Hydroxystaurosporine)** A cell-permeable Staurosporine (Cat. No.569397) derived anticancer agent that reversibly and ATP-competitively inhibits several protein kinases (IC_{50} = 29 nM, 34 nM, 30 nM, 590 nM and 530 nM for PKCα, PKCß, PKCγ, PKCδ and PKC; IC_{50} = 7 nM, 27 nM, 50 nM, 50 nM, 150 nM and 1.04 µM for Chk1, Cdc25C-associated protein kinase 1, Cdk1, PAK4, Cdk5/p25 and Chk2; IC_{50} = 33 nM, 50 nM, 95 nM, 500 nM, 500 nM and 1.0 µM for PDK1, lck, MAPKAP kinase-2, Akt, GSK-3ß and PKA, respectively). At higher concentrations (> 15 µM), affects the activities of Src, PIM-1, CKII, DNA-PK, ErK1, ILK-1 and MAPKK1). Reported to suppress thymidylate synthase expression, induce apoptosis with caspase activation, and sensitize tumor cells to a range of DNA-damaging agents.	500 µg
WHI-P180, Hydrochloride	**681500**	**[4-(3'-Hydroxyphenyl)amino-6,7-dimethoxyquinazoline, HCl]** A potent inhibitor of IgE-mediated mast cell responses to allergens *in vitro* and *in vivo*. Also inhibits cyclin-dependent kinase 2 (Cdk2; IC_{50} = 1 µM) by blocking the ATP site.	500 mg 1 µg

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 reverse transcriptases, which are RNA-dependent DNA polymerases that reverse transcribe the retroviral RNA genome into DNA.

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, 7-Amino-	**129935**	**(7-AAD; 7-Amino-AMD; 7-Aminoactinomycin C1; 7-Aminodactinomycin)** 7-Aminoactinomycin D, like its parent molecule, actinomycin D, is a DNA intercalator and has antibacterial properties. Exhibits growth-inhibitory activity against certain leukemias and sarcomas. Fluorescent excitation and emission maxima are 500 and 672 nm, respectively. Complexes with DNA and absorbs at 555 nm and emits at 655 nm. Useful in distinguishing early apoptotic cells, which have lost membrane integrity, from apoptotic and live cells. Has been used in DNA analysis and as a probe for chromosome structure and function.	1 mg
Actinomycin D, *Streptomyces* sp.	**114666**	**(Dactinomycin)** Anti-neoplastic antibiotic. Inhibits DNA-primed RNA polymerase by complexing with DNA via deoxyguanosine residues. At higher concentrations, DNA polymerase is inhibited. Also acts as a competitive inhibitor of serine proteases. Inhibits cell growth and colony formation in synchronized HeLa cells. Induces apoptosis in many cell lines. However, actinomycin D has also been shown to suppress etoposide-induced apoptosis in PC12 cells. Note: 1 set = 20 x 200 µg.	5 mg 1 set
α-Amanitin, *Amanita* sp.	**129741**	Toxic bicyclic octapeptide isolated from mushrooms. Acts as a potent and specific inhibitor of RNA polymerase II and messenger RNA synthesis in higher eukaryotes, including animals and plants.	1 mg
Aphidicolin	**178273**	A cell-permeable tetracyclic diterpene antibiotic that acts as a cell synchronization agent. Blocks the cell cycle at early S-phase. Specific inhibitor of DNA polymerase α and δ in eukaryotic cells and in some viruses. Potentiates apoptosis induced by arabinosyl nucleosides in leukemia cell lines. Also induces apoptosis in HeLa S3 cells, but inhibits vincristine-induced apoptosis in the p53-negative human prostate cancer cell line PC-3.	1 mg
DNA Polymerase Sliding Clamp Inhibitor, RU7	**260930**	*E. coli* **Pol III/ß-clamp Interaction Inhibitor** A 2-thio-thiazolidinone compound that binds the peptide-binding pocket of *E. coli* ß-clamp and disrupts *E. coli* DNA polymerase III binding to ß-clamp, but not the binding of Pol C to the ß-clamp of the gram-positive *Streptococcus pyogenes* species. Shown to selectively inhibit the polymerase activity of *E. coli* Pol III (K_i = 10 µM) over Pol II and IV in ß-dependent replicase assays, while exhibiting little effect toward the ß-independent activity of *E. coli* Pol I Klenow fragment or the yeast PCNA-dependent Pol δ activity of the *Saccharomyces cereviase* species.	25 mg
HSV Replication Inhibitor, BP5	**385883**	A cell-permeable sulfonamido-anthranilamide compound that displays antiviral properties. Acts by specifically disrupting the interaction between the catalytic subunit UL30 (Pol) and the processing subunit UL42 of herpes simplex virus DNA polymerase (IC_{50} = ~ 4 µM). Shown to prevent the long chain DNA synthesis mediated by Pol-UL42 versus Pol alone (IC_{50} = 26 µM vs. > 100 µM) and further inhibit both the plaque formation and virus yield in Vero cells by HSV-1 strain KOS (ED_{50} = 2 µM and 0.3 µM, respectively) with minimal cytotoxicity (IC_{50} = ~ 20 µM).	10 mg
Methyl α-Amanitin Oleate	**454559**	A semi-synthetic derivative of α-Amanitin, *Amanita* sp. (Cat. No.129741). It is about 30-fold more cell-permeable than α-Amanitin. Cytotoxic in concentrations of 10-100 nM. Useful for the study of the effect of α-Amanitin in living cells.	100 µg
Novobiocin, Sodium Salt	**491207**	DNA gyrase inhibitor used for the production of positively supercoiled plasma DNA. Inhibits retrovirus RNA-dependent DNA polymerases. Also a potent inhibitor of ADP ribosylation eliminates the wild-type pMG110 plasmid from *E. coli*.	1 g 10 g
Rifampicin	**557303**	**[3-(4-Methylpiperazinyliminomethyl)rifamycin SV; Rifampin]** Antibiotic that specifically inhibits DNA-dependent RNA polymerase in bacteria by forming an inactive complex. Does not affect mammalian RNA polymerase. Inhibits transcription by preventing the initial transcription complex from entering the elongation mode.	1 g 5 g
RNA Polymerase III Inhibitor	**557403**	**{N-[1-(3-(5-Chloro-3-methylbenzo[b]thiophen-2-yl-1-methyl-1H-pyrazol-5-yl)]-2-chlorobenzenesulfonamide; ML-60218}** A cell-permeable indazolo-sulfonamide compound that displays broad-spectrum inhibitory activity against RNA Polymerase III (IC_{50} = 27 and 32 µM for human and *S. cerevisiae* RNA Pol III, respectively). Inhibits cell growth in yeast by preventing RNA Pol III-mediated tRNA transcription.	10 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. Methylated DNA can trigger chromatin reorganization mediated by methyl-binding proteins. Four families of DNA methyltransferase genes have been identified in humans. They include *Dnmt1, Dnmt2,* and *Dnmt3b*, which encode proteins with different functional specificities. *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. *Dnmt3a* and *Dnmt3b* are strongly expressed in embryonic stem cells, but are down-regulated in differentiating embryonic stem cells and in adult somatic cells.

Most mammalian transcription factors bind GC-rich DNA elements, and methylation within these elements reduces their ability to bind. 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. Overexpression 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**	**(5-Aza-CdR; 5-Aza-dC; 5-Deoxy-2'-azacytidine)** A cytosine analog that acts as a DNA methyltransferase inhibitor. Restores caspase-8 and caspase-10 mRNA and protein expression as well as TRAIL (Tumor necrosis factor-Related Apoptosis Inducing Ligand) sensitivity in TRAIL-resistant cell lines. Also enhances apoptosis induced by HDAC (Histone Deacetylase) inhibitors.	25 mg
DNA Methyltransferase Inhibitor	**260920**	**2-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(1H-indol-3-yl)propionic acid; RG108** A cell-permeable, specific DNA methyltransferases inhibitor (IC_{50} = 115 nM for CpG methylase M.SssI) that displays anti-proliferative, but not cytotoxic, properties. Unlike the commonly used inhibitor 5-azacytidine, RG108 directly interacts with DNA methyltransferase active sit via its carboxy group.	10 mg
(–)-Epigallocatechin Gallate	**324880**	One of the main polyphenolic constituents of green tea that exhibits potent antitumor, anti-inflammatory, and antioxidant properties. Arrests cell cycling at G_0/G_1 phase and induces apoptosis in a dose-dependent manner. Shown to inhibit PMA-induced skin thickening and to activate of protein kinase C. Also activates ornithine decarboxylase and interleukin-1α mRNA and protein expression. Acts as an inhibitor of inducible nitric oxide synthase (iNOS) gene expression and enzyme activity. Also blocks peroxynitrite-mediated formation of 8-oxodeoxyguanosine and 3-nitrotyrosine. Strongly and directly inhibits telomerase in cell-free systems and in cancer cell lines. An inhibitor of D*nmt1* (IC_{50} = 210-470 nM). Acts as a selective and noncompetitive inhibitor of HAT activities (IC_{50} = 30, 50, 60 and 70 µM for p300, CBP, PCAF and TIP60) with minimal effects on HDAC, SIRT and HMTase.	10 mg
InSolution™Sinefungin	**567051**	An anti-leishmanial nucleoside antibiotic that acts as an S-adenosyl-L-methionine (SAM, AdoMet) methyltransferase-specific inhibitor.	2 mg

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Exonuclease Inhibitors

Product	Cat. No.	Comments	Size
MRN-ATM Pathway Inhibitor, Mirin	**475954**	**(Z)-5-(4-Hydroxybenzylidene)-2-imino-1,3-thiazolidin-4-one** A cell-permeable pyrimidinone compound that inhibits the exonuclease activity of Mre11, component of the MRN (Mre11-Rad50-Nbs1) complex, and prevents MRN-mediated activation of dimeric ATM (IC_{50} = 12 µM) in cell-free p53 Ser15 phosphorylation assays, while exhibiting little effect against MRN-independent ATM activation in the presence of high DSBs (DNA double strain breaks) or the activity of activated monomeric ATM. Mirin is shown to cause an increase of G2 population in exponentially growing TOSA4 cultures (~1.6-fold at 50 µM) and dramatically increase mitotic cell polulation (~10-fold at 25 µM) after irradiation of G2 phase U2OS cultures by preventing IR-induced G2/M checkpoint. Mirin exhibits no inhibitory activity against Rad50-associated adenylate kinase or Exonulease III.	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. In humans at least 16 different HDACs have been reported that are subdivided into Class I (HDAC 1, 2, 3, and 8); Class II (HDAC 4, 5, 6, 7, 9, and 10), and Class III (SIRT 1-7). Class I HDACs are widely expressed in tissues, and are primarily located in the nucleus. Class II HDACs are much larger in size and display limited tissue distribution. They can shuttle between the nucleus and cytoplasm. Class III HDACs consist of a large family of sirtuins (silent information regulators or SIR) that are evolutionarily distinct, with unique enzymatic mechanisms dependent on NAD^+. 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. HDAC inhibitors are also reported to induce the expression of pro-apoptotic Bak, down regulate the expression of anti-apoptotic Bcl-XL, and promote mitochondrial localization of Bax and Bak. They are also 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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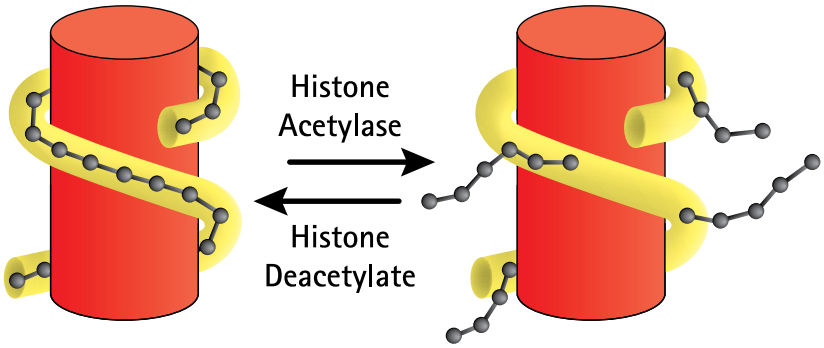

Histone Acetylase and Deacetylase Inhibitors

Product	Cat. No.	Comments	Size
Anacardic Acid	**172050**	**(AA; 2-Hydroxy-6-pentadecylbenzoic Acid; 6-Pentadecylsalicylic Acid)** A cell-permeable salicylic acid analog that acts as a potent, non-competitive inhibitor of p300 and PCAF (p300/CBP-associated factor) histone acetyltransferase activities (HAT; IC_{50} = ~8.5 µM and ~5 µM, respectively). Shown to affect HAT-dependent transcription from a chromatin template, but does not affect DNA transcription. Also reported to display a variety of biological activities, such as antibacterial, and antimicrobial action; and inhibition of prostaglandin synthase, tyrosinase, and lipoxygenase. Selectively enhances the activity of Aurora A.	10 mg
Apicidin, *Fusarium* sp.	**178276**	{*cyclo*-**[L-(2-Amino-8-oxodecanoyl)-L-(N-methoxytryptophan)-L-isoleucyl-D-pipecolinyl]**} A potent, cell-permeable inhibitor of histone deacetylase (IC_{50}= 700 pM for parasitic histone deactetylase) that also exibits antiprotozoal and potential anti-malarial properties. Inhibits HeLa cell proliferation (IC_{50}= 50-100 nM) and induces the transcriptional activation of p21 (WAF1). Also prevents H-*ras*-induced invasive phenotype of MCF10A cells possibly by down-regulating MMP-2.	1 mg 5 mg
Epigenetic Multiple Ligand	**324888**	**[3,5-bis(3,5-Dibromo-4-hydroxybenzylidene)-tetrahydro-2H-pyran-4-one]** A cell-permeable *bis*-arylidene compound that acts as an epigenetic multiple ligand (epi-ML) and inhibits substrates processing by several chromatin-associated enzymes, including H4/PRMT1 (91% inhibition at 50 µM), H4/RmtA (50% inhibition at 29 µM), H3/p300/CBP (61% inhibition at 50 µM), PABP1/CARM1 (>90% inhibition at 100 µM), H3/SET7 (>90% inhibition at 100 µM), SIRT1/2 (>50% inhibition at 25 µM), although the process of Np13p by PRMT1 is only weakly affected. Shown to induce either apoptosis (28% after 30 h incubation with 25 µM inhibitor) or granulocytic differentiation (100% of non-apoptotic cells after 30 hr incubation with 5 µM inhibitor) among U937 cell population.	10 mg
Histone Acetyltransferase Inhibitor II	**382110**	**[2,6-bis-(3-Bromo-4-hydroxybenzylidene)cyclohexanone]** A cell-permeable *bis*-arylidene cyclohexanone compound that acts as a p300/CBP-selective histone acetyltransferase inhibitor (IC_{50} = 5 µM), while it affects GCN5 and PCAF only at much higher concentrations (30% and 0% inhibition, respectively, at 5 µM inhibitor concentration). Shown to decrease histone H3 acetylation (IC_{50} ≤ 40 µM) and induce chromatin condensation in HeLa cells.	10 mg
Histone Deacetylase Inhibitor II	**382148**	**(*m*-Carboxycinnamic Acid bis-Hydroxamide; CBHA)** A cell-permeable second generation hybrid polar agent that acts as a histone deacetylase (HDAC) inhibitor. The HDAC inhibition is believed to arise as a result of the binding of the hydroxamic moiety to the active site zinc. Shown to be a potent inducer of transformed cell growth arrest and terminal differentiation (~4 µM). Induces apoptosis and the CD95/CD95-Ligand expression in human neuroblastoma.	5 mg
Histone Deacetylase Inhibitor III	**382149**	**[4-Dimethylamino-*N*-(6-hydroxycarbamoylhexyl)benzamide; *N*-Hydroxy-7-(4-dimethylaminobenzoyl)aminoheptanamide; M344]** A cell-permeable amide analog of Trichostatin A (Cat. No.647925) that potently inhibits histone deacetylases (IC_{50} = 40 nM for rat liver HDAC and IC_{50} = 100 nM for maize HD). Induces differentiation and inhibits proliferation (~2 µM) of murine erythroleukemia cells.	1 mg 5 mg
Histone Deacetylase Inhibitor IV	**382170**	**[N^1-(2-Aminophenyl)-N^7-phenylheptanediamide]** A cell-permeable pimeloylanilide compound that acts as a *FXN*- (frataxin gene) specific HDAC (histone deacetylase) inhibitor. Reverses the silencing of *FXN* transcription in FRDA (Friedreich's ataxia) cells (~3-fold increase of *FXN* mRNA at 5 µM in primary FRDA lymphocytes and ~3-fold frataxin expression in FRDA cell line at 2.5 µM) due to hypoacetylation of histones H3 and H4 by increasing acetylation at H3K14, H4K5 and H4K12, without significant changes in acetylation at H3K9, H4K8 and H4K16. In comparison, Trichostatin-A (Cat. No.647925 and647926) and SAHA, two other commonly used HDAC inhibitors, exhibit no effect on *FXN* transcription.	10 mg
Histone Deacetylase Inhibitor VI, HNHA	**382172**	**[HNHA; N-Hydroxy-7-(2-naphthylthio)heptanomide]** A cell-permeable hydroxyamide-based SAHA analog that potently inhibits histone deacetylase (HDAC) activity (IC_{50} = 100 nM). Shown to induce histone acetylation and p21 transcription with concomitent inhibition of cell cycle progression in human fibrosarcoma HT1080 cells. Reported to be more potent than SAHA in inhibiting tumor growth in a murine xenograph model *in vivo*.	10 mg

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Histone Acetylase and Deacetylase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Histone Deacetylase Inhibitor VII, 106	**382173**	**[Pimelic Diphenylamide 106; N^1-(2-Aminophenyl)-N^7-p-tolylheptanediamide]** A cell-permeable *p*-tolylbenzamide and a Histone Deacetylase (HDAC) Inhibitor IV (Cat. No.382170) analog that acts as a selective inhibitor against class I HDAC1,2,3 (IC_{50} = 0.15, 0.76, and 0.37 µM with 15, 30, and 180 min preincubation, respectively), while exhibiting much lower acitivity against class I HDAC8 ($IC_{50} \geq 5$µM with 3 h preincubation) and no activity against class II HDAC4/5/7 even at concentrations as high as 180µM. Although the mode of inhibition is mechanistically competitive and reversible, due to the slow- and tight-binding nature, long preincubation is often required for effective *in vitro* enzyme inhibition, while 106-induced cellular H3 hyperacetylation is shown to persist for more than 6 hours after inhibitor removal by washing in GM15850 culture. 106 is reported to be less cytotoxic than TSA (Cat. No.647925), MS-275, and SAHA (EC_{50} = 6.3, 0.328, 0.768, and 1.5 µM, respectively, in GM15850 killing).	5 mg
ITSA1	**419840**	**[N-(1H-Benzotriazol-1-yl)-2,4-dichlorobenzamide; Inhibitor of Trichostatin A 1]** A cell-permeable benzotriazole amide that counteracts and complements histone and tubulin deacetylase (HDAC and TDAC) inhibitors. Inhibits tubulin acetylation mediated by Trichostatin A, but not by Taxol. Through its successful use with TSA *in vivo*, it was shown that the expression of Rhodopsin-GFP transgene in Zebrafish eye is regulated via a mechanism involving reversible histone acetylation.	25 mg
InSolution™Leptomycin A, *Streptomyces* sp.	**431051**	**(ATS1287 A; LMA)** A cell-permeable antifungal antibiotic that acts as an inhibitor of nuclear export. Inhibits nucleocytoplasmic translocation of Rev at nanomolar concentrations.	1 µg
InSolution™Leptomycin B, *Streptomyces* sp.	**431050**	**(LMB)** An antifungal antibiotic that acts as an inhibitor of nuclear export because of its ability to interact with and impair the function of the nuclear export factor CRM1. It is about twice as potent as Leptomycin A (Cat. No.431051) in inhibiting nucleocytoplasmic translocation of Rev, blocks the Rev-dependent export of mRNA into cytoplasm, and suppresses HIV-1 replication in primary human monocytes (IC_{50} = 600 pM). In addition, LMB effectively induces the accumulation of p53 in the nucleus of normal fibroblasts as well as protects p53 from Mdm2-mediated ubiquitination and degradation.	5 µg
Oxamflatin	**499700**	**{(2*E*)-5-[3-(Phenylsulfonylamino)phenyl]pent-2-en-4-ynohydroxamic Acid}** A cell-permeable, aromatic sulfonamide derivative with a hydroxamic acid group that potently inhibits mammalian histone deacetylase (IC_{50} = 15.7 nM) by binding to the active site Zinc. Augmented the expression of transcription factor JunD and causes an inhibition of transformation in K-*ras*-transformed NIH3T3 cells (MIC = ~ 40 nM). Upregulates plasminogen activator inhibitor type 2 (PAI-2) expression with concomitant inhibition of urokinase (u-PA) gene and protein expression in HT-1080 and U-937 cells. Elevates the expression of extracellular matrix proteins fibronectin and gelsolin.	1 mg 5 mg
InSolution™Ratjadone A, Synthetic	**553590**	A cell-permeable polyketide that displays potent antitumor properties in eukaryotes. 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. Inhibits proliferation ($IC_{50} \leq 1$ ng/ml) and induces cell cycle arrest at G1 phase.	2 µg
SBHA	**559418**	**(Suberic Bishydroxamate; Suberoyl Bishydroxamic Acid)** A cell-permeable bishydroxamic acid histone deacetylase (HDAC) inhibitor with anti-tumor properties. Causes an increase in acetylated histone H4 in MEL cells and inhibits the human HDAC1 and HDAC3 activities with a similar potency (ID_{50} ~ 250-300 nM). Belongs to the hybrid polar class of compounds that acts both as inducers of differentiation of transformed cells and apoptosis. Suppresses the growth of proliferating keratinocytes and squamous cell carcinoma cells (IC_{50} = 11.57 µM and 5.39 µM, respectively).	100 mg
Scriptaid	**565730**	**{CGK1026; 6-(1,3-Dioxo-1*H*,3*H*-benzo[*de*]isoquinolin-2-yl)-hexanoic Acid Hydroxyamide** A relatively non-toxic, cell-permeable hydroxamic acid-containing histone deacetylase (HDAC) inhibitor. Facilitates transcriptional activation (TGFß/Smad4) in both stable and transient receptor assays in a concentration-dependent manner. At ~2 µg/ml (6-8 µM) concentrations, results in a greater than 100-fold increase in histone acetylation in PANC-1 cells. Reported to derepress hTERT by inhibiting the recruitment of HDAC into E2F-pocket protein complexes assembled on the hTERT promoter.	5 mg
SIRT1 Inhibitor III	**566322**	**(6-Chloro-2,3,4,9-tetrahydro-1H-carbazole-1-carboxamide, racemic)** A cell-permeable indole compound that acts as a potent and highly selective inhibitor of SIRT1 (IC_{50} = 98 nM). It inhibits other sirtuin family deacetylases only at much higher concentrations (IC_{50} = 19.6 and 48.7 µM for SIRT2 and SIRT3, respectively) and shows no inhibitory effect against class I and II HDACs or NAD glycohydrolase even at concentrations as high as 100 µM. Shown to be orally bioavailable with a serum half-life of 136 minutes in mice *in vivo*.	5 mg

Histone Acetylase and Deacetylase Inhibitors *continued*

Product	Cat. No.	Comments	Size
SIRT1 Inhibitor IV	**566325**	**{(S)-35; (6S)-2-Chloro-5,6,7,8,9,10-hexahydro-cyclohepta[b]indole-6-carboxamide}** A cell-permeable entiomerically pure compound that is structurally similar to and exhibits similar potency (IC_{50} = 63 nM) and selectivity as SIRT1 Inhibitor III (Cat. No.566322). Shown to be orally bioavailable with a serum half-life of 94 min in mice *in vivo*.	500 µg
SIRT1/2 Inhibitor IV, Cambinol	**566323**	**[NSC-112546; 5-(2-Hydroxy-naphthalen-1-ylmethyl)-6-phenyl-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one]** A cell-permeable ß-naphthol compound that inhibits the NAD-dependent deacetylase activity of hSIRT1 and hSIRT2 (IC_{50} = 56 µM and 59 µM, respectively) in a substrate-, but not NAD-, competitive manner. It inhibits SIRT5 deacetylase activity only at much higher concentrations (IC_{50} >300 µM) and exhibits no inhibition against class I and II HDACs. Cambinol-induced apoptosis in BCL6-expressing Burkitt lymphoma cell lines has been attributed to the hyperacetylation of BCL6 and p53. Shown to effectively inhibit xenografted Daudi Burkitt lymphoma growth in mice *in vivo*.	5 mg
SIRT1/2 Inhibitor VIII, Salermide	**566330**	**[N-(3-((2-Hydroxynaphthalen-1-ylmethylene)-amino)-phenyl)-2-phenyl-propionamide]** A cell-permeable 2-hydroxy-naphthaldehyde that acts as an inhibitor against sirtuins SirT1 and SirT2, members of class III HDACs. Salermide effectively inhibits the activity of both SirT1 and SirT2 (by 80% at 100 and 25 µM, respectively), while its structural analogue Sirtinol (Cat. Nos.566320 and566321), at 100 µM concentration, inhibits SirT2 only by up to 60% and is of no effect against SirT1. Salermide is also shown to be at least 2-fold more potent than Sirtinol (both at 100 µM) in killing leukemia KG1A and lymphoma Raji cultures.	10 mg
SIRT2 Inhibitor	**566324**	**[Sirtuin 2 Inhibitor; AGK2; 2-Cyano-3-(5-(2,5-dichlorophenyl)-2-furanyl)-N-5-quinolinyl-2-propenamide]** A cell-permeable quinoline compound that targets the nicotinamide-binding site and acts as a reversible sirtuin 2- (SIRT2) selective inhibitor (IC_{50} = 3.5 µM) with little activity against SIRT1/3 (IC_{50} >50 µM). Prevents cellular α-tubulin deacetylation in HeLa cells in a dose-dependent manner and with little cytotoxic effect. Shown to rescue α-Synuclein-mediated toxicity both in primary rat embryo midbrain cultures *in vitro* and in a *Drosophila* PD model *in vivo*. The inactive isomer AGK7 (Cat. No.566326) can be used as a negative control.	5 mg
SIRT2 Inhibitor, Inactive Control, AGK7	**566326**	A cell-permeable structural isomer of SIRT2 Inhibitor, AGK2 (Cat. No.566324) that selectively inhibits sirtuin 3 over sirtuins 1 and 2 (IC_{50} = >5 µM, >50 µM and >50 µM for SIRT3, SIRT1 and SIRT2, respectively) and poorly affects both α-synuclein-mediated toxicity and α-Syn aggregation in α-Syn-H4 cells.	5 mg
Sirtinol	**566320**	**{2-[(2-Hydroxynaphthalen-1-ylmethylene)amino]-N-(1-phenethyl)benzamide; Sir Two Inhibitor Naphthol}** A cell-permeable 2-hydroxy-1-naphthaldehyde derivative that acts as a specific and direct inhibitor of the sirtuin class of deacetylase activity with no affect on human HDAC1 (IC_{50} = 48 µM, 131 µM and 58 µM for ySir2, hSIRT1 and hSIRT2, respectively). Reported to inhibit Sir2p transcriptional silencing activity *in vivo* (IC_{50} = 25 µM), and NAD-dependent histone deacetylase activity of purified recombinant yeast Sir2p and human SIRT2 *in vitro* (IC_{50} = 70 µM and 40 µM, respectively). A 10 mM (1 mg/254 µl) solution of Sirtinol (Cat. No.566321) in DMSO is also available.	5 mg
InSolution™Sirtinol	**566321**	**{2-[(2-Hydroxynaphthalen-1-ylmethylene)amino]-N-(1-phenethyl)benzamide; Sir Two Inhibitor Naphthol}** A 10 mM (1 mg/254 µl) solution of Sirtinol (Cat. No. 566320) in DMSO.	1 mg
Splitomicin	**567750**	**(1,2-Dihydro-3H-naphtho[2,1-b]pyran-3-one)** A cell-permeable lactone derived from ß-naphthol that acts as a 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
Tenovin-1	**580566**	**N-(4-*tert*-Butylbenzoyl)-N'-(4-acetylaminophenyl)-thiourea** A cell-permeable benzoylthiourea compound that acts as a reversible inhibitor of class III HDAC sirtuins against SirT2 (IC_{50} = ~ 10 µM). Based on studies using the more soluble analog Tenovin-6, Tenovin-1 is expected not to compete with substrate binding and display lower potency against SirT1/3 (IC_{50} = 21/67 µM using Tenovin-6). Tenovin-1 (10 µM) up-regulates cellular p53 protein, but not mRNA, level in MCF-7 (≥6-fold in 6 h), presumably by blocking mdm2-mediated p53 degradation. Two day Tenovin-1 treatment (10 µM) results in selective killing of cancer cells with functional p53, but not p53-lacking cancer cells or normal human dermal fibroblasts. Despite its low aqueous solubility, administration of Tenovin-1 suspension is shown to effectively reduce BL2 and ARN8 xenographs in mice *in vivo* (≥50% reduction with 92 mg/kg, daily, i.p.).	10 mg

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Histone Acetylase and Deacetylase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Trichostatin A, *Streptomyces* sp.	**647925**	**(4,6-Dimethyl-7-[*p*-dimethylaminophenyl]-7-oxahepta-2,4-dienohydroxamic Acid; TSA)** A potent and reversible, cell-permeable inhibitor of histone deacetylase. Blocks cell cycle progression at the G_1 phase in HeLa cells and induces a 12-fold increase in intracellular levels of gelsolin. Induces reversion of oncogenic *ras*-transformed NIH/3T3 cells to a normal morphology. Inhibits IL-2 gene expression (IC_{50} = 73 nM) in Jurkat cells and shows immunosuppressive activity in a mouse model. Down-regulates $p57^{kip2}$ in Hep 3B cells. A 10 mM (500 µg/165 µl) solution of Trichostatin A, *Streptomyces* sp. (Cat. No.647926) in DMSO is also available.	1 mg
InSolution™Trichostatin A, *Streptomyces* sp.	**647926**	A 10 mM (500 µg/165 µl) solution of Trichostatin A, *Streptomyces* sp. (Cat. No. 647925) in DMSO.	500 µg
Valproic Acid, Sodium Salt	**676380**	**(2-Propylpentanoic Acid, Na)** A cell-permeable, short-chained 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. At therapeutic levels (0.35 mM - 1.04 mM), causes inositol depletion, inhibits both GSK-3α and -3ß, activates ERK pathway and produces neurotropic effects. Has been used as an anti-epileptic agent. Also reported to stimulate peroxisome proliferator-activated receptor (PPAR) activity. Displays a potent teratogenic activity in humans and rodent models.	5 g

Nuclease Inhibitors

Product	Cat. No.	Comments	Size
Aurintricarboxylic Acid	**189400**	A cell-permeable polyanionic, polyaromatic compound used as a powerful inhibitor of cellular processes that are dependent on the formation of protein-nucleic acid complexes. Binds to aFGF and reduces its angiogenic activity. Shown to inhibit apoptotic cell death in various cell types induced by a variety of factors. ATA is a potent inhibitor of DNA topoisomerase II (IC_{50}= 75 nM for the yeast enzyme as measured by relaxation assays) that also acts as a potent inhibitor of angiogenesis. Inhibits von Willebrand factor binding to platelets and reduces glutamate-induced neuronal injury. ATA stimulates the tyrosine phosphorylation of MAP kinases, Shc proteins, phosphatidylinositol 3-kinase, and phospholipase Cγ. Inhibits both major calpain isoforms (IC_{50} = 22 µM and IC_{50} = 10 µM for µ-calpain and m-calpain, respectively).	100 mg
Diethyl Pyrocarbonate	**298711**	**DEPC, Diethyl Oxydiformate** Inhibits ryanodine binding to ryanodine/Ca^{2+} receptor channel in skeletal muscle in a dose- and time-dependent manner and increases the Ca^{2+} permeability of SR vesicles. Useful for specific inactivation of nucleases during isolation of undegraded polynucleotides. Also inhibits platelet-activating factor acetyl hydrolase. Has been used as a probe for the topography of 5.8S rRNA in yeast ribosomes.	25 g 100 g
DNA Base Excision Repair Pathway Inhibitor	**262015**	**[7-Nitroindole-2-carboxylic acid]** A cell-permeable, potent, specific, and nontoxic inhibitor of the DNA repair enzyme, APE1 (human apurinic/apyrimidinic endonuclease; IC_{50} = ~3 µM). Shown to target the APE1 active site and inhibit its 3'-phosphodiesterase and 3'-phosphatase activities. Exhibits minimal effects on endonuclease IV, BamH1 restriction endonuclease, or topoisomerase I even at concentration as high as 100 µM. Also shown to potentiate the cytotoxicity of several DNA damaging agents, such as MMS, temozolomide, Zeocin, and H_2O_2 in HeLa, HT1080, and MDA-MB-231 cells.	25 mg
DNA Repair Pathway Inhibitor, NS-123	**323115**	**4'-Bromo-3'-nitropropiophenone** A cell-permeable nitro-propiophenone compound that preferentially enhances tumor growth-inhibitory effects of ionizing radiation (~ 5 µM in U251, HT-29 and A549 tumor cells and in U251 xenograft mouse model, 50 mg/kg, i.p.) with no apparent effect on normal human glial cells, Zebrafish embryos and nude mice. Shown to increase the accumulation of unrepaired double-strand DNA breaks and prolong the damage-dependent signaling.	25 mg
Ribonuclease Inhibitor, Human, Recombinant, *E. coli*	**556881**	Recombinant, human ribonuclease inhibitor expressed in *E. coli*. Non-competitive inhibitor that inactivates RNase by non-covalent binding. Has been used to improve cDNA synthesis and *in vitro* RNA synthesis, increase yields of polysomes, and aid in the preparation of RNase-free antibodies. Inhibits RNases A, B, and C. Does not inhibit RNase T_1 and S1 nuclease from *Aspergillus*.	2500 U

p53 Inhibitors

Product	Cat. No.	Comments	Size
Pifithrin-α, p-Nitro	**506152**	**[1-(4-Nitrophenyl)-2-(4,5,6,7-tetrahydro-2-imino-3(2H)-benzothiazolyl)ethanone, HBr]** A cell-permeable p53 inhibitor that serves as the prodrug form of Pifithrin-α, *p*-Nitro, Cyclic (Cat. No.506154). Although its *in vitro* efficacy (ED_{50} = 0.3 µM in protecting etoposide-induced cortical neuron death) is similar to that of Pifithrin-α (Cat. No.506132), it is 100-fold more potent than Pifithrin-α when adminstered in rats *in vivo* due to its long-lasting, steady conversion to the corresponding cyclic form of active compound in biological systems ($t_{1/2}$ = 8h in neuron culture medium at 37°C).	5 mg
Pifithrin-α, p-Nitro, Cyclic	**506154**	**{2-(4-Nitrophenyl)imidazo[2,1-b]-5,6,7,8-tetrahydrobenzothiazole}** A cell-permeable p53 inhibitor that exhibits 10-fold higher potency (ED_{50} = 30 nM in protecting etoposide-induced cortical neuron death) and 50% longer half-life ($t_{1/2}$ = 6h in neuron culture medium at 37°C) than Pifithrin-α (Cat. No.506132). However, despite its *in vitro* efficacy, this inhibitor is not effective when adminstered in rats *in vivo*. For *in vivo* applications, please consider Pifithrin-α, *p*-Nitro (Cat. No.506152).	5 mg
Pifithrin-µ	**506155**	**(Phenylacetylenylsulfonamide)** A cell-permeable sulfonamide that blocks p53 interaction with Bcl-xL and Bcl-2 proteins and selectively inhibits p53 translocation to mitochondria without affecting the transactivation function of p53. Effectively protects against γ radiation-induced cell death *in vitro* and animal lethality *in vivo*. Because Pifithrin-µ targets only the mitochondrial branch of the p53 pathway without affecting the important transcriptional functions of p53, it is superior to Pifithrin-α (Cat. No.506132) in *in vivo* studies. Shown to selectively interact with inducible HSP70 and disrupt its functions.	10 mg

Tautomerase Inhibitor

Product	Cat. No.	Comments	Size
MIF Antagonist, ISO-1	**475837**	**[(S,R)-3-(4-Hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid, methyl ester; Macrophage Migration Inhibitory Factor Antagonist, ISO-1]** A cell-permeable isoxazoline compound that displays anti-inflammatory properties. Inhibits MIF tautomerase activity by binding to its catalytic active site (IC_{50} = 7 µM for D-dopachrome tautomerase) and suppresses the production of TNFα, PGE_2 and COX-2 in human monocytes, and arachidonic acid in RAW 264.7 macrophages. Shown to exhibit antidiabetogenic properties in immunoinflammatory diabetic mouse model.	5 mg

Telomerase Inhibitors

Telomerase is a specialized ribonucleoprotein composed of a catalytic subunit telomerase reverse transcriptase (TERT), its intrinsic RNA template (TERC) and associated proteins, such as dyskerin, NOP10, NHP2, and GAR1. Its main function is to stabilize telomeres that protect chromosomes from recombination, end-to-end fusion, and recognize damaged DNA. In addition, telomeres control the replicative capability of cells. With each cell division some of the DNA is lost from the ends of chromosomes. This is due to the fact that the conventional DNA polymerase can not fully replicate the 3' end of the lagging strands of the linear molecule. When telomeres reach a critical minimum length, senescence is induced, which coincides with the activation of p53, p21, and p16 in cells. This leads to cell growth arrest and apoptosis. Telomerase preserves telomere length by adding hexameric (TTAGGG) repeats to the ends of chromosomes, thereby circumventing the cumulative damage that occurs with each mitotic cell division. Telomerase recognizes the G-rich strand of an existing telomere repeat sequence and elongates it in the 5′-to-3′ direction.

Dysregulation of telomerase expression has been linked to several human diseases. For example, dyskeratosis congenita results from telomerase dysfunction due to mutations in either hTR or the telomerase RNA-associated protein dyskerin. These patients show visibly shorter telomeres than normal individuals. About 90% of cancer cells contain short telomeres, but exhibit high telomerase activity. For example, 75% of oral carcinomas, 80% of lung cancers, 93% of breast cancers, and 95% of colorectal cancers, have detectable telomerase activity. 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.

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. Although telomerase inhibitors can accelerate senescence and apoptotic cell death, they may also destroy normal proliferating cells and stem cells.

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Telomerase Inhibitors

Product	Cat. No.	Comments	Size
3'-Azido-3'- deoxythymidine	**194348**	**(AZT)** Inhibitor of HIV-1 reverse transcriptase that blocks the incorporation of nucleotides into growing DNA strands. Useful for antiviral and anticancer studies. Enters CNS by diffusion and causes irreversible telomere shortening.	10 mg
InSolution™AZT, Triphosphate, Tetralithium Salt	**194950**	**(AZTTP)** A reverse transcriptase inhibitor that acts by docking to the active site of HIV reverse transcriptase. It's inhibitory effect is greater during the initiation phase of reverse transcription. Also reported to inhibit telomerase activity *in vitro* (IC_{50} = 30 µM). Acts synergistically with Cisplatin (Cat. No.232120) to inhibit cell proliferation in some cell lines.	1 µmol
3'-Deoxy-2',3'- didehydrothymidine	**257920**	A reverse transcriptase (RT) inhibitor with antiviral properties. Has been shown to cause a consistent and rapid telomere shortening in vegetatively growing *Tetrahymena*. Reduces the proliferation of Jurkat and L1210 cell lines as well as human peripheral blood mononuclear cells at ~250 µM level. In combination with 5-fluorouracil, d4T yields supra-additive cytotoxic effects in colon cancer (WiDr) and breast cancer (MCF-7) cell lines.	25 mg
(–)-Epigallocatechin Gallate	**324880**	**{EGCG; (2R,3R)-2-(3,4,5-Trihydroxyphenyl)-3,4-dihydro-1[2H]-benzopyran-3,5,7-triol-3-(3,4,5-trihydroxybenzoate)}** One of the main polyphenolic constituents of green tea that exhibits potent antitumor, anti-inflammatory, and antioxidant properties. Arrests cell cycling at G_0/G_1 phase and induces apoptosis in a dose-dependent manner. Shown to inhibit PMA-induced skin thickening and to activate of protein kinase C. Also activates ornithine decarboxylase and interleukin-1α mRNA and protein expression. Acts as an inhibitor of inducible nitric oxide synthase (iNOS) gene expression and enzyme activity. Also blocks peroxynitrite-mediated formation of 8-oxodeoxyguanosine and 3-nitrotyrosine. Strongly and directly inhibits telomerase in cell-free systems and in cancer cell lines. An inhibitor of D*nmt1* (IC_{50} = 210-470 nM). Acts as a selective and noncompetitive inhibitor of HAT activities (IC_{50} = 30, 50, 60 and 70 µM for p300, CBP, PCAF and TIP60) with minimal effects on HDAC, SIRT and HMTase.	10 mg
PIPER	**528120**	**{N,N'-*bis*[2-(1-Piperidino)ethyl]-3,4,9,10-perylenetetracarboxylic Diimide; Telomerase Inhibitor IV}** 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. May also be useful as an antiproliferative agent.	10 mg
Telomerase Inhibitor III, Sodium Salt	**581004**	**[5'-d(TTAGGG)-3'; TAG-6]** A short, cell-permeable hexameric phosphorothioate oligonucleotide (PS-ODN) telomere mimic that inhibits telomerase activity in cell lysates and lengthens cell doubling time *in vitro* and *in vivo* at concentrations of less than 2.5 µM. Note: 150 nmol = 285 µg.	150 nmol
Telomerase Inhibitor IX	**581011**	**[N,N'-bis(2,3-Dihydroxybenzoyl)-1,3-phenylenediamine; MST-312]** A cell-permeable, bis-catechol containing, *m*-phenylenediamide compound that displays anti-proliferative properties. Acts as a potent, reversible inhibitor of telomerase activity (IC_{50} = 670 nM, 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
Telomerase Inhibitor VI, Sodium Salt	**581006**	**(5'-CAGUUAGGGUUAG-3'; 2'-O-MeRNA)** 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). Induces apoptosis in cationic lipid treated human epithelial cells. Note: 100 nmol = 469 µg.	100 nmol
TMPyP4	**613560**	**[*meso*-5,10,15,20-Tetrakis-(N-methyl-4-pyridyl)porphine, Tetratosylate]** 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 intensely in the presence of quadruplex DNA.	25 mg

Topoisomerase Related 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. The catalytic cycle of the enzyme consists of DNA cleavage to form a covalent enzyme-DNA intermediate, DNA relaxation, and re-ligation of the phosphate backbone to restore the continuity of the DNA. 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. On the other hand, differentiated cells have relatively low topoisomerase II levels and are much more resistant to the action of these inhibitors.

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Topoisomerase Related Inhibitors

Product	Cat. No.	Comments	Size
Acetyl-11-keto-ß- Boswellic Acid, *Boswellia serrata*	**110123**	**(3-O-Acetyl-11-keto-ß-Boswellic Acid; AKBA; AKßBA)** A cell-permeable pentacyclic triterpene of the ursane type that displays anti-tumor and anti-inflammatory properties. Shown to block the phosphorylation and degradation of IκBα and inhibit NF-κB-mediated gene transcription in chemoresistant, androgen-independent PC-3 prostate cancer cells (~10 µM). Mobilizes intracellular Ca^{2+} and stimulates the activation of p42/44 and p38 MAPKs (~30 µM in human PMN) and increases the formation of reactive oxygen species. Also reported to induce apoptosis and act as a non-redox, non-competitive inhibitor of 5-lipoxygenase (IC_{50} = 1.5 µM in rat PMNLs), and topoisomerase I (≥ 10 µM in calf thymus). When complexed with γ-cyclodextrin to facilitate its delivery, AKßBA has been demonstrated to exhibit *in vivo* efficacy in tumor growth and inhibition.	5 mg
AG 1387	**658520**	**[AG 555, 5-Iodo; α-Cyano-(3,4-dihydroxy)-5-iodo-N-(3-phenylpropyl)cinnamide; 2-Cyano-3-(3,4-dihydroxy-5-iodo-phenyl)-N-(3-phenylpropyl)acrylamide]** A reversible and substrate competitive 5-iodo analog of tyrphostin AG 555 (Cat. No.658404) that displays anticancer and antiviral properties. Reported to be more cell-permeable and potent than AG 555 as an inhibitor of protein tyrosine kinase and DNA topoisomerase I (TOPO I). In contrast to Camptothecin, *Camptotheca acuminata* (Cat. No.208925), AG 1387 inhibits the DNA relaxation activity of TOPO I by interacting with and preventing its binding to DNA. Also blocks and prevents murine AIDS (MAIDS) development by affecting both viral and/or cellular targets.	5 mg
Aurintricarboxylic Acid	**189400**	**(ATA)** A cell-permeable polyanionic, polyaromatic compound used as a powerful inhibitor of cellular processes that are dependent on the formation of protein-nucleic acid complexes. Binds to aFGF and reduces its angiogenic activity. Shown to inhibit apoptotic cell death in various cell types induced by a variety of factors. ATA is a potent inhibitor of DNA topoisomerase II (IC_{50}= 75 nM for the yeast enzyme as measured by relaxation assays) that also acts as a potent inhibitor of angiogenesis. Inhibits von Willebrand factor binding to platelets and reduces glutamate-induced neuronal injury. ATA stimulates the tyrosine phosphorylation of MAP kinases, Shc proteins, phosphatidylinositol 3-kinase, and phospholipase Cγ. Inhibits both major calpain isoforms (IC_{50} = 22 µM and IC_{50} = 10 µM for µ-calpain and m-calpain, respectively).	100 mg

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Topoisomerase Related Inhibitors *continued*

Product	Cat. No.	Comments	Size
Camptothecin, 10-Hydroxy-, *Camptotheca acuminata*	**390238**	**(HCPT; 10-Hydroxycamptothecin)** A cell-permeable powerful DNA topoisomerase I inhibitor. Reduces DNA synthesis *in vitro* in murine hepatoma cells. Has selective inhibitory effect on the phosphorylation of histone H1 and H3, but less effect on other histones.	25 mg
Camptothecin, *Camptotheca acuminata*	**208925**	**{4-Ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b] quinoline-3,14(4H,12H)dione}** A cell-permeable DNA topoisomerase I inhibitor. Exhibits anti-leukemic and antitumor properties. Induces apoptosis in HL-60 cells and mouse thymocytes. Arrests cells at the G_2/M phase.	50 mg
Daunorubicin, Hydrochloride	**251800**	**(Daunomycin, HCl)** Potent cell-permeable anticancer agent whose potential target site may be mitochondrial cytochrome *c* oxidase. Has been shown to inhibit RNA and DNA synthesis. Inhibits eukaryotic topoisomerases I and II. Induces DNA single-strand breaks. Also induces apoptosis in HeLa S3 tumor cells.	5 mg
Doxorubicin, Hydrochloride	**324380**	**(Adriamycin; 14-Hydroxydaunomycin, HCl)** Antitumor antibiotic and a highly effective myotoxin that inhibits topoisomerase II (IC_{50} = 100 nM). Binds to nucleic acids, presumably by specific intercalation into the DNA double helix, thereby inhibiting nucleic acid synthesis. Induces apoptosis in rhabdomyosarcoma cell lines.	10 mg
Ellagic Acid, Dihydrate	**324683**	**(4,4',5,5',6,6'-Hexahydroxydiphenic Acid 2,6,2',6'-Dilactone)** A cell-permeable, reversible, potent antioxidant that has anti-mutagenic and anti-carcinogenic properties. Acts as a selective and ATP-competitive inhibitor of CK2 (IC_{50} = 40 nM). Moderately inhibits DNA topoisomerases I and II, Lyn, PKA catalytic subunit, Lyk, GSK-3, PKC, and FGR (IC_{50} = 1.8, 2.1, 2.9, 3.5, 4.3, 7.5, 8.0, and 9.4 µM, respectively). Only minimally inhibits DYRK1a, CSK, RET, Flt3, and NPM-ALK (IC_{50} >40 µM). Shown to act as an uncompetitive inhibitor of arginine methyltransferase CARM1 and block histone H3R17 methylation.	500 mg
Ellipticine	**324688**	**(5,11-Dimethyl-6H-pyrido[4,3-b]carbazole)** A cell-permeable antitumor alkaloid that acts as an inhibitor of topoisomerase II and acts as an intercalative agent that stimulates topoisomerase II-mediated DNA breakage. Is also capable of uncoupling mitochondrial oxidative phosphorylation.	10 mg
Epirubicin Hydrochloride	**324905**	**(4'-Epidoxorubicin, HCl)** A cell-permeable antitumor antibiotic. A stereoisomer of Doxorubicin (Cat. No.324380) that exhibits reduced cardiotoxicity. Its antitumor actions are mediated by targeting topoisomerase II.	5 mg
Etoposide	**341205**	**(VP-16)** A cell-permeable derivative of podophyllotoxin that acts as a topoisomerase II inhibitor (IC_{50} = 59.2 µM) has major activity against a number of tumors, including germ cell neoplasms, small cell lung cancer, and malignant lymphoma. Induces apoptosis in mouse thymocytes and in HL-60 human leukemia cells.	25 mg
Genistein	**345834**	**(4',5,7-Trihydroxyisoflavone)** A cell-permeable, reversible, substrate competitive inhibitor of protein tyrosine kinases, including autophosphorylation of epidermal growth factor receptor kinase (IC_{50} = 2.6 µM). The inhibition is competitive with respect to ATP and non-competitive with respect to the phosphate acceptor. Has only a trivial effect on the activity of PKA and PKC (IC_{50} > 350 µM). Inhibits tumor cell proliferation and induces tumor cell differentiation. Produces cell cycle arrest and apoptosis in Jurkat T-leukemia cells. However, it prevents anti-CD3 monoclonal antibody-induced thymic apoptosis. Also inhibits topoisomerase II activity *in vitro*.	20 mg 50 mg
Merbarone	**445800**	**[NSC-336628; 5-(N-Phenylcarboxamido)-2-thiobarbituric Acid]** A cell-permeable anticancer drug that inhibits the catalytic activity of topoisomerase II (topo II) without damaging DNA or stabilizing DNA-topo II cleavable complexes (IC_{50} = 20 µM for purified mammalian topo II versus IC_{50} = ~ 200 µM for topo I). Also induces apoptosis in human leukemic CEM cells through a caspase-3-like protease-dependent mechanism.	25 mg
Suramin, Sodium Salt	**574625**	A reversible and competitive inhibitor of protein tyrosine phosphatases. An anti-neoplastic, anti-angiogenic agent that uncouples G-proteins from receptors presumably by blocking their interaction with intracellular receptor domains. Inhibits GDP-GTP exchange, the rate limiting step in the activation of G_α-subunits. A competitive inhibitor of reverse transcriptase. Reported to inhibit topoisomerases I and II. Inhibits Ca^{2+}-ATPase in sarcoplasmic reticulum membranes. Also inhibits the cell-surface binding of various growth factors, including EGF, PDGF, and TGF-ß. An inhibitor of phospholipase D (IC_{50} = 15 µM). Reported to interact with ATP-binding enzymes and P_2-purinergic receptors. An effective inhibitor of angiogenesis in the calmodulin assay when given in combination with angiostatic steroids.	50 mg 200 mg

ATM/ATR Kinases

ATM (Ataxia-telangiectasia mutated) and ATR (ATM- and Rad3-related), members of phosphatidyl inositol 3-kinase-like kinase (PIKK) family, are activated in response to DNA damage. ATM is primarily activated in response to double-strand breaks (DSBs) induced by ionizing radiation and radiomimetic drugs, while ATR acts in response to UV damage. ATR is reported to bind to UV-damaged DNA with greater affinity than to undamaged DNA. Also, damaged DNA stimulates the ATR kinase activity to a significantly higher level than does undamaged DNA. ATM and ATR are usually found localized near the damaged regions within several minutes indicting that these two kinases may also have a damage-sensing role.

After their recruitment to sites of DNA damage, ATM and ATR phosphorylate several intracellular substrates, including Chk1 and Chk2 that in turn target other proteins to induce cell-cycle arrest and allow DNA repair to proceed. In normal cells ATM is present as inert dimers or multimers, which dissociate into highly active ATM monomers following any DNA damage. During this process, ATM undergoes autophosphorylation on Ser[1981] and the activated ATM undergoes additional phosphorylations and acetylation reactions. It is believed that after rapid activation of ATM and subsequent phosphorylation of its substrates, ATR is independently activated and maintains phosphorylation of these substrates.

Defects in ATM/ATR signaling pathways are commonly seen in human cancer cells and affect the sensitivity of tumors to DNA-damaging chemo- and radiation therapies. In addition, most cancer cells have defective checkpoints that allow the cell cycle to proceed even in the presence of DSBs caused by ionizing radiation and radiomimetic drugs. Hence, designing drugs that block ATM and ATR activties might be useful in promoting chemo- and radiation sensitization in checkpoint-deficient cancer cells.

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ATM Kinase Inhibitors

Product	Cat. No.	Comments	Size
ATM Kinase Inhibitor	**118500**	**(2-Morpholin-4-yl-6-thianthren-1-yl-pyran-4-one)** A cell-permeable disubstituted pyranone compound that acts as a potent and ATP-competitive inhibitor of ATM kinase (IC_{50} = 13 nM; K_i = 2.2 nM). Displays excellent selectivity over other PIKK family kinases (IC_{50} = 2.5 , 9.3 , 16.6 µM for DNA-PK, mTOR, PI 3-K, respectively; IC_{50} > 100 = µM for PI 4-K and ATR) and exhibits little activity towards a panel of 60 other kinases even at concentrations as high as 10 µM. Inhibits ATM-dependent cellular protein phosphorylation following ionizing radiation (IR) and sensitizes cells with wild-type ATM, but not mutant ATM, to the cytotoxic effects of IR and DNA-damaging agents. A 10 mM (2 mg/506 µl) solution of ATM Kinase Inhibitor (Cat. No.118502) in DMSO is also available.	2 mg
InSolution™ATM Kinase Inhibitor	**118502**	A 10 mM (2 mg/506 µl) solution of ATM Kinase Inhibitor (Cat. No. 118500) in DMSO.	2 mg
ATM/ATR Kinase Inhibitor	**118501**	**(CGK 733)** A cell-permeable thiourea compound that selectively inhibits the kinase activity of ATM and ATR (IC_{50} = ~ 200 nM) without significant effect against other PIKK family members (PI 3-K, mTOR, and DNA-PK) or kinases that are known to phosphorylate p53 (ERK, CK1, Cdk2, JNK, PKC, CAK, Chk1, PKR, and p38). Shown to reverse senescence in human primary BJ and HMEC cells. Unlike LY 294002 (Cat. No.440202 and440204), this inhibitor does not interfere with cellular PI 3-K/PDK1/Akt signaling pathway.	5 mg

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DNA-Dependent Protein Kinase (DNA-PK) Inhibitors

DNA-dependent protein kinase (DNA-PK) is a trimeric nuclear serine/threonine kinase composed of a large catalytic subunit and two DNA-targeting proteins, Ku70 and Ku80. The catalytic subunit, by itself, is inactive. It relies on other DNA-PK components to direct it to the DNA and trigger its kinase activity. The amino acid sequence of the DNA-PK suggests that it is a member of the phosphatidylinositol-3-kinase (PI 3-K) superfamily. DNA-PK recognizes and initiates repair of DNA double-strand breaks produced by ionizing radiation and certain drugs.

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} leading to stabilization and inhibition of p53 degradation by MDM2. 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 MDM2 protein. Phosphorylation of Ser^{15} weakens both the association of p53 with MDM2 and the repression of p53 by MDM2. Phosphorylation of DNA-PK by the PKC_{δ} catalytic fragment leads to the dissociation of DNA-PK from DNA, resulting in its inactivation. More recently, DNA-PK has been reported to suppress also a p53-independent apoptotic response to DNA damage.

DNA-PK represents a new target for cancer drug development. 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. A number of small molecule inhibitors of DNA-PK catalytic subunit have been developed, which sensitize cells to DNA-damaging agents, but are relatively nontoxic in the absence of DNA breaks. These inhibitors may have clinical potential in the treatment of cancer.

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DNA-Dependent Protein Kinase (DNA-PK) Inhibitors

Product	Cat. No.	Comments	Size
Compound 401	**234501**	**{2-(Morpholin-1-yl)pyrimido[2,1-a]isoquinolin-4-one}** A cell-permeable pyrimido-isoquinolinone compound that acts as a potent, reversible, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 280 nM) with ~19-fold selectivity over mTOR (IC_{50} = 5.3 µM). Exhibits much reduced or no activity against 43 other commonly studied kinases, including PI 3-K, ATM, and ATR. Shown to induce apoptosis and inhibit mTOR-dependent growth in $TSC1^{-/-}$ murine embryo fibroblasts.	5 mg
DNA-PK Inhibitor	**260960**	**(4,5-Dimethoxy-2-nitrobenzaldehyde; DMNB; DNA-Dependent Protein Kinase Inhibitor)** A cell-permeable vanillin derivative that acts as a potent and selective inhibitor of DNA-PK (DNA-dependent protein kinase) activity (IC_{50} = 15 µM) and DNA-PK-mediated DSB (double strand break) DNA repair by NHEJ (non-homologous DNA-end-joining). Shown to effectively sensitize cells to killing by Cisplatin (Cat. No.232120). Does not affect PKC or Chk2 kinase activities.	10 mg
DNA-PK Inhibitor II	**260961**	**{DNA-Dependent Protein Kinase Inhibitor II; 2-(Morpholin-4-yl)-benzo[h]chromen-4-one; NU7026}** A cell-permeable benzochromenone compound that acts as a potent, specific, reversible, and ATP-competitive inhibitor of DNA-PK with an IC_{50} of 0.23 µM. It is highly selective towards DNA-PK over PI3K-related kinases (IC_{50} = 13 µM for PI 3-K and > 100 µM for ATM and ATR) and has no effect on PARP-1. Inhibits DNA-PK-mediated, but not PARP-1-mediated, cellular DNA DSB (double strand break) repair and PLDR (potentially lethal damage recovery) following IR (ionizing radiation). Shown to sensitize both proliferating and quiescent cells to IR.	5 mg
DNA-PK Inhibitor III	**260962**	**[1-(2-Hydroxy-4-morpholin-4-yl-phenyl)ethanone; IC86621]** A cell-permeable aryl-morpholino compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 120 nM) and PI 3-Kinase catalytic subunit p110ß (IC_{50} = 135 nM). It inhibits DNA-PK-mediated cellular DNA DSB (double strand break) repair (EC_{50} = 68 µM) and enhances DSB-induced antitumor activity both *in vitro* and *in vivo*, while exhibiting no cytotoxic effects (up to 50 µM) in the absence of DSBs. It inhibits PI 3-K p110α, p110γ, and p110δ only at much higher concentrations (IC_{50} = 1.4, 0.88, and 1.0 µM, respectively) and exhibits no effect against a panel of several other kinases, including, Cdk2, Src, PKA, PKC, Chk1, CK1, ATM, and FKBP12, even at concentrations as high as 100 µM.	1 mg

DNA-Dependent Protein Kinase (DNA-PK) Inhibitors *continued*

Product	Cat. No.	Comments	Size
DNA-PK Inhibitor IV	**260963**	**(2-Hydroxy-4-morpholin-4-yl-benzaldehyde; IC60211)** A morpholino-salicylaldehyde compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 430 nM). Inhibits PI 3-K catalytic subunit p110-isozymes at higher concentrations (IC_{50} = 10 µM, 2.8 µM, 5.1 µM and 37 µM for α, ß, δ and γ, respectively) and weakly inhibits a panel of several other kinases, including, ATM, CK2, GRK2, mTOR, PI 3KC2α, PI 3KC2ß, PI 3KC2γ and PI 4Kß, even at concentrations as high as 50 µM.	1 mg 5 mg
DNA-PK Inhibitor V	**260964**	**[AMA37; ArylMorpholine Analog 37; 1-(2-Hydroxy-4-morpholin-4-yl-phenyl)- henyl-methanone]** A morpholino-benzophenone compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 270 nM). Inhibits PI 3-K catalytic subunit p110-isozymes at higher concentrations (IC_{50} = 32 µM, 3.7 µM, 22 µM and ~ 100 µM for α, ß, δ and γ, respectively) and weakly inhibits a panel of several other kinases, including, ATM, ATR, CK2, GRK2, mTOR, PI 3KC2α, PI 3KC2ß, PI 3KC2γ and PI 4Kß, even at concentrations as high as 50 µM.	1 mg 5 mg

MDM2: The Regulator of p53 Degradation

MDM2, a p53-inducible phosphoprotein, binds to the N-terminus of the p53 and negatively regulates its activity. *Mdm2* is a p53 responsive gene and its transcription can be activated by p53. Hence, in the presence of high levels of p53, MDM2 levels are also elevated. p53 interacts with MDM2 at Phe[19], Trp[23], and Leu[26] to fill up a complementary hydrophobic pocket of MDM2. The three amino acids are also essential for transactivation of p53. Binding of MDM2 to p53 antagonizes the transcriptional activity of p53 and blocks its acetylation and transactivation by interfering with p300/CBP.

MDM2 is believed to function as an E3 ligase to ubiquitinate p53 and force its export from the nucleus to the cytoplasm where it is degraded in the proteasome. Some researchers believe that E3 ubiquitin ligase activity of MDM2 alone is not sufficient to trigger p53 degradation, because MDM2 mono-ubiquitinates p53 at multiple sites, but does not catalyze the addition of polyubiquitin chains that are essential for recognition by the proteasome. One possibility exists that mono-ubiquitination of p53 exposes a nuclear export signal and polyubiquitination and degradation can then proceed in the cytoplasm. Although p53-mediated transactivation is a nuclear event, p53 degradation occurs in the cytoplasm. Hence, ubiquitin ligase function of MDM2 could serve as a cellular mechanism for turnover of p53-MDM2 complexes after their function is completed. It is generally agreed that the nuclear export signal of MDM2 is required for p53 degradation. Studies have shown that Leptomycin B that blocks nuclear export complex formation also prevents nuclear-cytoplasmic shuttling of MDM2 and p53 and p53, if sequestered in the cytoplasm, is resistant to degradation by MDM2. Import of p53 from cytoplasm to nucleus and export back to cytoplasm seems to be essential for its degradation, and the shuttling of MDM2 and p53 may be a mechanism to prevent their premature degradation.

Malignant tumors, particularly breast tumors and soft tissue sarcomas, are reported to frequently over-express MDM2. In breast cancer cells, over-expression of MDM2 is correlated with lack of p21 expression. However, over-expression of MDM2 in normal cells is known to cause G_1 arrest. Hence, MDM2 induced by DNA damage in normal cells may have a protective role in preventing untimely cell cycle progression.

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MDM2 Inhibitors

Product	Cat. No.	Comments	Size
MDM2 Antagonist II, NSC 66811	**444144**	**7-(Anilino(phenyl)-methyl)-2-methyl-8-quinolinol** A cell-permeable, non-peptidyl, quinolinol compound that binds MDM2 with high affinity (K_i = 120 nM) and disrupts MDM2-p53 interaction. Shown to dose-dependently induce cellular accumulation of p53, MDM2, and p21 in HCT-116 human colon cancer cell line with wild-type p53.	1 mg 10 mg
MDM2 Antagonist, Nutlin-3, Racemic	**444143**	A cell-permeable *cis*-imidazoline compound that acts as a potent and selective MDM2 antagonist (IC_{50} = 90 nM for Nutlin-3a and 13.6 µM for Nutlin-3b) and displays antitumor properties. Activates p53 pathway by binding MDM2 in the p53-binding pocket and inhibits MDM2-p53 interaction. Shown to suppress tumor growth by induction of apoptosis in several cancer cells with wild-type p53 and in xenografted tumor mice. A 10 mM (1 mg/172 µl) solution of MDM2 Antagonist, Nutlin-3, Racemic (Cat. No.444151) in DMSO is also available.	1 mg
MDM2 Inhibitor	**444145**	***trans*-4-Iodo, 4'-boranyl-chalcone** A cell-permeable boranyl-chalcone that binds strongly to MDM2 and irreversibly disrupts MDM2/p53 protein complex. Exhibits selective toxicity towards MDM2 overexpressing human breast cancer cell lines (IC_{50} = 10, 8.8, and 7 µM for MDA-MB-435, MDA-MB-231, and Wt-MCF7, respectively) compared to normal breast cell lines (IC_{50} = 75 and 63 µM for MCF-10A and MCF-12A, respectively).	10 mg

Acetyl-CoA Carboxylase (ACC) Inhibitors

Product	Cat. No.	Comments	Size
CoEnzyme A, Trilithium Salt	**234101**	A cofactor in enzymatic acetyl transfer reactions.	100 mg
TOFA	**613450**	**5-(Tetradecyloxy)-2-furoic acid** A cell-permeable furoic acid compound that acts as a potent, reversible, and competitive inhibitor of acetyl-CoA carboxylase (ACC), a key enzyme involved in the fatty acid biosynthesis. Inhibits cellular fatty acid synthesis in a dose-dependent manner (IC_{50} = 4 µM in human breast cancer cell line MCF7). TOFA-induced reduction in malonyl-CoA is reported to off-set the effect of C75 (Cat. No.341325) on food intake in fasted mice and on apoptosis in tumor cells.	5 mg

Ceramide Kinase Inhibitors

Product	Cat. No.	Comments	Size
Ceramide Kinase Inhibitor, K1	**219489**	**(F-12509A Cyclic Product K1)** A cell-permeable tetracyclic quinone compound that acts as a specific, reversible, and non-competitive inhibitor of CerK (ceramide kinase) activity (IC_{50} = ~5 µM) with little effect against SPHK1/2 or DGKγ (IC_{50} > 100 µM). Shown to reduce cellular C1P (ceramide-1-phosphate) synthesis by 40% at ≥ 20 µM in a rat basophilic leukemia cell line RBL-2H3 and block CerK-mediated degranulation in both RBL-2H3 and murine BMMC (bone marrow-derived mast cells) in a dose-dependent manner. Exhibits no cytotoxic effect against RBL-2H3 even at concentrations as high as 100 µM.	1 mg

Cyclooxygenase (COX) Inhibitors

Cyclooxygenases (COXs), also known as prostaglandin H synthases, are fatty acid oxygenases that contain about 600 amino acid residues and act on arachidonic acid to generate prostaglandins (PG). All vertebrates contain two COX genes: one encoding the constitutive COX-1 and another inducible COX-2. COX-1 and COX-2 share approximately 60-65% amino acid identity. These COX isoforms are bifunctional hemoproteins that catalyze both the bioxygenation of arachidonic acid to form PGG_2 and the peroxidative reduction of PGG_2 to form PGH_2. Hence, the catalytic domain of COX is considered to contain both cyclooxygenase and peroxidase active sites. The peroxidase site is required for the activation of heme groups that participate in the cyclooxygenase reaction. The active site of COX-2 is slightly larger and can accommodate bigger structures than those that are able to reach the active site of COX-1.

COX-1 is an ubiquitously and constitutively expressed enzyme that is associated with the endoplasmic reticulum (ER). It is responsible for maintaining normal physiologic functions and is considered as a “housekeeping” enzyme. It is normally expressed in the gastrointestinal tract, kidneys, and platelets and appears to be responsible for mediating the production of thromboxane A2 and prostaglandins. COX-2 is an inducible enzyme and is generally present at very low levels. It is 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. The lumen of the ER is important for both the structure and function of COXs: its oxidative potential allows formation of the disulfide bonds of the enzymes and the N-linked glycosylation, which occurs in the ER, appears to be necessary for proper folding of the enzyme.

Most 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 the COX-2 activity. COX-2 inhibitors have the potential to provide the traditional benefits of NSAID with significantly reduced incidence of endoscopic ulcers. Hence, they offer greater therapeutic promise in the treatment of inflammation and cancer. 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. Increased expression of COX-2 has been associated with increased incidence of colon and

breast cancers. It is over-expressed in about 50% of adenomas and 85% of adenocarcinomas of the colon. Hence, COX-2 inhibitors offer greater therapeutic promise not only in the treatment of inflammation, but also some forms of cancer.

More recently, there has been an upsurge of interest in COX-2 inhibitors as possible candidates for the treatment of Alzheimer's disease. This is due to the fact that researchers have begun to think about "inflammation as a factor" in the development and/or progression of Alzheimer's disease. Studies have shown that aggregated synthetic Ab_{1-40} peptide induces COX-2 expression in SH-SY5Y neuroblastoma cells and also stimulates oxygenase and peroxidase activities of COX-2 in a cell free system. Since neuronal excitation and oxidative stress have been linked to the pathogenesis of several neurodegenerative disorders, inhibiting excessive COX-2 activity may reduce the oxidative stress-induced neuronal damage and trauma.

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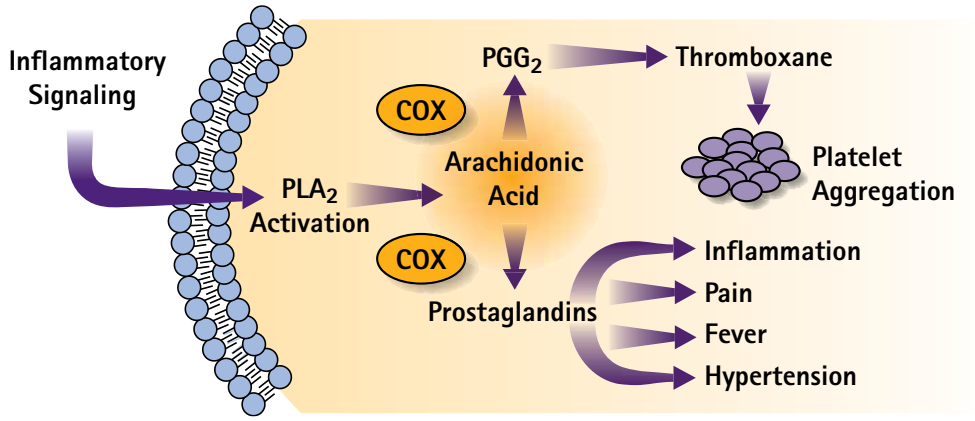

Cyclooxygenase (COX) Inhibitors

Product	Cat. No.	Comments	Size
COX-1 Inhibitor II	**236006**	**[4-Amino-(N-(4-cholorophenyl)-N-methyl)benzenesulfonamide]** A cell-permeable benzenesulfonalide compound that acts as a catalytic site-targeting, COX-1-selective inhibitor (IC_{50} = 3.2 µM and > 100 µM for COX-1 and COX-2, respectively). Shown to exhibit similar *in vivo* analgesic activity as aspirin, but not the gastric disturbance effects commonly seen with aspirin and indomethacin (Cat. No.405268).	25 mg
COX-1 Inhibitor IV, TFAP	**236007**	**N-(5-Amino-2-pyridinyl)-4-trifluoromethylbenzamide** A cell-permeable pyridinyl-benzamide compound that acts as a COX-1-selective inhibitor (IC_{50} = 0.80 and 210 µM against ovine COX-1 and COX-2, respectively) by targeting the enzyme's active site and displays analgesic properties in mice and rats *in vivo* (30 mg/kg, p.o.) without long-term cytotoxic effects (300 mg/kg in mice, daily, p.o. for 14 days). Unlike COX-2-inhibiting analgesics such as aspirin, TFAP is shown not to cause gastric damage in rats *in vivo* (300 mg/kg, p.o.).	10 mg
COX-1 Inhibitor, FR122047	**236005**	**{4,5-Bis(4-methoxyphenyl-2-[(1-methylpiperazin-4-yl)carbonyl] thiazole, Hydrochloride; 1-[(4,5-Bis(4-methoxyphenyl-2-thiazoyl) carbonyl]-4-methylpiperazine, Hydrochloride; FR 122047}** A cell-permeable trisubstituted thiazole compound that acts as a potent and selective inhibitor of COX-1 (IC_{50} = 28 nM and 65 µM for human recombinant COX-1 and COX-2, respectively). Displays ~2,300 fold greater selectivity towards inhibition of COX-1 over COX-2. Reported to be orally active and display analgesic, anti-platelet and anti-inflammatory properties.	5 mg
COX-2 Inhibitor I	**236011**	**{LM-1685; Methyl [5-methylsulfonyl-1-(4-chlorobenzyl)-1H-2-indolyl]carboxylate}** A cell-permeable potent and selective inhibitor of COX-2 from human monocytes (IC_{50} = 650 nM) and in whole blood (IC_{50} = 4.3 µM). 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

Cyclooxygenase (COX) Inhibitors *continued*

Product	Cat. No.	Comments	Size
COX-2 Inhibitor II	**236012**	**{4-[(5-Difluoromethyl-3-phenyl)-4-isoxazolyl]benzenesulfonamide; SC-791}** 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*. Has been used extensively in various animal models to study the role of COX-2 in wound healing process.	5 mg
COX-2 Inhibitor III	**236013**	**[BTB 02472; N-(5-Acetyl-2-piperidinophenyl)-N'-(2,5-dichlorophenyl)thiourea]** A thiourea compound that acts as an active-site-targeting COX-2 inhibitor. Exhibits better selectivity than Nimesulide and Celecoxib (% inhibition of COX-1 and COX-2 at 10.0 µM inhibitor concentration = 5.1 and 26.36 with BTB 02472; 9.87 and 19.94 with Nimesulide; 12.35 and 40.37 with Celecoxib).	25 mg
COX-2 Inhibitor IV	**236014**	**{SPB 04674; 5-(4-Methoxyphenyl)-3,7-dimethyl-4,5-dihydroisoxazolo[4,5-d]pyridazin-4-one}** A pyridazinone compound that acts as an active-site-targeting COX-2 inhibitor with a potency and selectivity (inactive against COX-1 vs. 33.85% inhibition of COX-2 at 10.0 µM inhibitor concentration) comparable to that of Rofecoxib.	25 mg
COX-2 Inhibitor V	**236015**	**[FK3311; 4'-Acetyl-2'-(2,4-Difluorophenoxy)methanesulfonanilide]** A cell-permeable and orally available sulfonanilide that acts as a COX-2-selective non-steroidal anti-inflammatory drug (NSAID). Shown to exhibit 500-fold greater potency in inhibiting the LPS-induced (IC_{50} = 316 nM in human mononuclear cells) than the non-induced/constitutive (IC_{50} = 160 µM in human platelets) TxB2 production *in vitro* and effectively alleviate warm ischemia-reperfusion injury in the canine liver and rat lung *in vivo*.	5 mg
Curcumin, *Curcuma longa* L.	**239802**	**[1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]** A cell-permeable and irreversible antitumor and anti-inflammatory agent that acts as an inhibitor of 5-lipoxygenase (IC_{50} = 8 µM) and cyclooxygenase (IC_{50} = 52 µM). Confers significant protection against neurotoxic and genotoxic agents. Also inhibits the induction of nitric oxide synthase in activated macrophages (IC_{50} = 6 µM). Recently shown to inhibit the EGF receptor intrinsic kinase activity in the human epidermoid carcinoma A431 cells in a dose- and time-dependent manner. Also shown to be a p300/CREB-binding protein-specific inhibitor of histone acetyltransferase, inhibiting the acetylation of histones H3 and H4 with an IC_{50} of ~25 µM. Does not affect p300/CREB binding protein-associated factor (PCAF).	100 mg
Cyclooxygenase Inhibitor Set	**239783**	Contains 100 mg of Meloxicam (Cat. No.444800), 5 mg of NS-398 (Cat. No.349254), 5 mg of SC-560 (Cat. No.565610), and 5 mg of Sulindac Sulfide (Cat. No.574102).	1 set
Diclofenac Sodium	**287840**	**{2-[(2,6-Dichlorophenyl)amino]benzeneacetic Acid, Na}** A cell-permeable, non-selective cyclooxygenase inhibitor (IC_{50} = 60 nM and 200 nM for ovine COX-1 and COX-2 respectively) and potent non-steroidal anti-inflammatory drug with analgesic activity. Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. Also inhibits liver phenol sulfotransferase activity (IC_{50} = 9.5 µM).	1 g
Diclofenac, 4'-Hydroxy-	**287845**	**{2-[((2',6'-Dichloro-4'-hydroxy)phenyl)amino]benzeneacetic Acid; 4'-OHD}** Cell-permeable. One of the major metabolites of the non-steroidal anti-inflammatory drug Diclofenac (Cat. No.287840). Regioselectively formed through oxidation of diclofenac by cytochrome P450 2C9. Suppresses prostaglandin E_2 (PGE_2) formation by specifically blocking COX-2 activity (IC_{50} = 16.9 nM).	100 µg
DuP-697	**317500**	**5-Bromo-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)thiophene** A potent, cell permeable, 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 min respectively) than COX-1 (IC_{50} = 9 µM). DuP-697 also attenuates the COX-1 inhibitory activity of non-selective COX inhibitors such as Indomethacin (Cat. No.405268).	5 mg
Ebselen	**324483**	**[2-Phenyl-1,2-benzisoselenazol-3(2H)-one; PZ51]** A cell-permeable, non-selective inhibitor of COX-1 and COX-2. An excellent scavenger of peroxynitrite. Glutathione peroxidase mimetic. Inhibits radiation-induced apoptosis in thymocytes by scavenging peroxides. A neuroprotective agent active against acute focal ischemic injury. Inhibits LPS-induced NF-κB nuclear translocation and LPS-induced phosphorylation of JNK.	5 mg
ETYA	**434741**	**(5,8,11,14-Eicosatetraynoic Acid)** Cell permeable. Inhibits arachidonic acid uptake and the activities of arachidonic acid specific and non-specific acyl-CoA synthetases. Inhibits phospholipase A_2 (PLA_2) and cytochrome P-450. Inhibits cyclooxygenase (ID_{50} = 8 µM), 5-lipoxygenase (ID_{50} = 10 µM), 12-lipoxygenase (ID_{50} = 300 nM), and 15-lipoxygenase (ID_{50} = 200 nM) in whole cells. Also acts as a potent modulator of Ca^{2+} entry into cells. Blocks monocyte binding in minimally-oxidized LDL in endothelial cells. Stimulates luteinizing hormone release from cultured pituitary cells.	20 mg

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Cyclooxygenase (COX) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Flurbiprofen	**344079**	**{(±)-2-Fluoro-a-methyl[1,1'-biphenyl]-4-acetic Acid; U-27182}** A mixture of S(+) and R(–) enantiomers. A cell-permeable, non-steroidal anti-inflammatory agent that acts as a potent inhibitor of cyclooxygenase (IC_{50} = 5 nM for LPS-induced COX in human peripheral blood cells). Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. Suppresses iNOS expression in RAW 264.7 macrophages. Reduces microglial activation and ß-amyloid deposit in APP+PS1 transgenic mice.	100 mg
(±)-Ibuprofen	**401003**	**{[(±)-2-(4-Isobutylphenyl)-propionic Acid}** A nonsteroidal anti-inflammatory drug (NSAID) that acts as a reversible and competitive inhibitor of cyclooxygenase 1 (COX-1) (IC_{50} = 4.85 µM). Inhibits COX-2 at higher concentrations (IC_{50} = 223 µM). Blocks aspirin inactivation of COX-1 (EC_{50} antagonism of 200 µM aspirin = 290 nM). Shown to reduce the total Aß secretion (Amyloid $ß_{40\ and\ 42}$) in human neuronal cells and offers neuroprotection against glutamate-, nitric oxide-, and superoxide-induced damage. Reported to activate peroxisome proliferator-activated receptors (PPAR) α and γ in both CV-1 and C3H10T1/2 cells (~100 µM-500 µM).	1 g
Indomethacin	**405268**	**[1-(*p*-Chlorobenzoyl)-2-methoxy-3-methyl-1H-indole-3-acetic Acid]** A non-steroidal anti-inflammatory, cell permeable, antipyretic agent. Non-selective COX inhibitor (IC_{50} = 740 nM for COX-1; IC_{50} = 970 nM for COX-2). Inhibits phospholipase A_2 (IC_{50} = 145 µM). Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation and suppresses production of Aß-peptide and secreted form of APP by inhibition of APP mRNA levels in NG108-15 cells.	10 g
Indomethacin Ester, 4-Methoxyphenyl-	**405271**	**[1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic Acid, 4-Methoxyphenyl Ester]** A cell-permeable 4-methoxyphenyl ester derivative of the non-steroidal anti-inflammatory drug (NSAID) Indomethacin (Cat. No.405268) that acts as a potent and selective inhibitor of COX-2 (IC_{50} = 40 nM) compared to COX-1 (IC_{50} > 66 µM).	5 mg
Kaempferol	**420345**	**(3,4',5,7-Tetrahydroxyflavone)** A cell-permeable phytoestrogen that inhibits topoisomerase I-catalyzed DNA religation in HL-60 cells. Offers protection against $Aß_{25-35}$-induced cell death in neonatal cortical neurons. Its protective effects are comparable to that of estradiol. Blocks the Aß-induced activation of caspase-2, -3, -8, and -9, and reduces NMDA-induced neuronal apoptosis. Reported to be a potent inhibitor of monoamine oxidases. Acts as an inhibitor of COX-1 activity (IC_{50} = 180 µM), and of transcriptional activation of COX-2 (IC_{50}<15 µM).	25 mg
Meloxicam	**444800**	**[4-Hydroxy-2-methyl-N-(5-methyl-2-thiazoyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide]** A cell-permeable, non-steroidal anti-inflammatory drug (NSAID) of the oxicam family which preferentially inhibits the inducible isoform of COX-2 (IC_{50} = 4.7 µM) relative to COX-1 (IC_{50} = 36.6 µM). Also inhibits the growth of colorectal cancer cells *in vitro*.	100 mg
5-Nitro-2-(3-phenylpropyl-amino)benzoic Acid	**484100**	**(NPPB)** Potent Cl^- channel blocker (IC_{50} = 100 nM-100 µM), depending on channel subtype and assay method. Inhibits cyclooxygenase (IC_{50} = 8 µM).	10 mg
NS-398	**349254**	**[N-(2-Cyclohexyloxy-4-nitrophenyl)methanesulfonamide]** A cell-permeable selective inhibitor of COX-2 *in vitro*. Inhibits sheep placental COX-2 (IC_{50} = 3.8 µM) while COX-1 activity is unaffected at concentrations up to 100 µM. Displays potent anti-inflammatory and analgesic activity *in vivo* in rat at concentrations from 0.3 to 5 mg/kg.	5 mg
Pterostilbene, *Pterocarpus marsupium*	**523310**	**(*trans*-3,5-Dimethoxy-4'-hydroxystilbene)** A cell-permeable methoxylated analog of Resveratrol (Cat. No.554325) that displays antioxidant, antiproliferative, and hypoglycemic properties. Moderately inhibits COX-1 and -2 activities (IC_{50} = 19.8 µM and 83.9 µM) respectively, induces apoptosis in HL60 cells (IC_{50} = 70 µM), prevents DMBA-induced preneoplastic lesions (ED_{50} = 4.8 µM) and decreases plasma glucose level in streptozotocin-induced diabetic rats comparable to that of Metformin.	10 mg
Radicicol, *Diheterospora chlamydosporia*	**553400**	A cell-permeable, ATP-site binding, and irreversible antifungal macrocyclic lactone antibiotic that acts as a protein tyrosine kinase inhibitor. Inhibits $p60^{v\text{-}src}$ kinase activity (IC_{50} = 0.27 nM). Inhibits the expression of COX-2 (IC_{50} = 27 nM) without affecting COX-1 expression in LPS-stimulated macrophages. Disrupts K-Ras-activated signaling pathways by selectively depleting Raf kinase. Inhibits tyrosine phosphorylation of $p53/56^{lyn}$ in LPS-stimulated macrophages. Suppresses NIH/3T3 cell transformation by diverse oncogenes such as *src*, *ras*, and *mos* in part by blocking the key signal transduction intermediates such as MAP kinase and GAP-associated p62. Also exhibits anti-angiogenic activity *in vivo*. Inhibits Wnt-5A expression in dermal papilla cells (IC_{50} = 190 nM).	500 µg

Cyclooxygenase (COX) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Resveratrol	**554325**	**(*trans*-3,4',5-Trihydroxystilbene)** A phenolic product found in both grape skins and wines. Has antifungal, antitumor, and antioxidative properties. A specific inhibitor of cyclooxygenase-1 (COX-1; ED_{50} = 15 µM). Also inhibits the hydroxyperoxidase activity of COX-1 (ED_{50} = 3.7 µM). Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. Inhibits phorbol ester-induced free radical formation in HL-60 cells (ED_{50} = 27 µM) and acts as an anti-mutagenic agent (ED_{50} = 15 µM) in TM677 cells treated with DMBA. Also a selective inhibitor of P450 1A1. Reported to activate sirtuins and promote the survival of eukaryotic cells.	25 mg
SC-560	**565610**	**[5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole]** A cell-permeable, 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
SKF-86002	**567305**	**{6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridyl)imidazo[2,1-b]thiazole}** A cell-permeable, reversible, and ATP-competitive cytokine-suppressive anti-inflammatory drug (CSAID). A bicyclic imidazole that inhibits lipolysaccharide (LPS)-stimulated human monocyte IL-1 and TNF-α production (IC_{50} = 1 µM). Also acts as an inhibitor of both cyclooxygenase and 5-lipoxygenase. SKF-86002 also acts as a specific p38 MAP kinase inhibitor.	5 mg
Sodium Salicylate	**567630**	**(NaSal; Salicylic Acid, Na)** A cell-permeable, non-steroidal anti-inflammatory agent that interferes with TNF-induced NF-κB activation by inhibiting phosphorylation and subsequent degradation of the IκB-α protein. Selectively inhibits TNF-induced activation of p42 (ERK2) and p44 (ERK1) MAP kinases. Also inhibits TNF-induced activation of JNK. Induces apoptosis via p38 kinase activation. Inhibits COX-2 and inducible NOS (iNOS) transcription independently of NF-κB activation.	5 g
Sulindac Sulfide	**574102**	**{(Z)-5-Fluoro-2-methyl-1-[*p*-(methylthio)benzylidene]indene-3-acetic Acid}** A cell-permeable, active metabolite of Sulindac (Cat. No.574100). Strongly inhibits Ras-induced malignant transformation and Ras/Raf-dependent transactivation. Also decreases the Ras-induced activation of c-Raf-1 kinase. Inhibits growth and induces apoptosis in prostate cancer cell lines. Selectively inhibits COX-1 (ID_{50} = 500 nM) compared to prostaglandin H synthase-2 (PGHS-2; COX-2; ID_{50} = 14 µM). Preferentially inhibits the secretion of $Aß_{42}$ in CHO cells stably transfected with both APP_{75}, and the PS1 mutant M146L.	5 mg
Sulindac Sulfone	**574105**	**{Exisulind; FGN-1; (Z)-5-Fluoro-2-methyl-1[*p*-(methylsulfonyl)benzylidene]indene-3-acetic Acid}** A cell-permeable sulfone metabolite of Sulindac (Cat. No.574100) that has anticancer properties but lacks cyclooxygenase (COX) inhibitory activity. Also inhibits cell growth and induces apoptosis.	5 mg

Diacylglycerol (DAG) kinase Inhibitors

Product	Cat. No.	Comments	Size
Diacylglycerol Kinase Inhibitor I	**266785**	**6-{2-{4-[(*p*-Fluorophenyl)phenylmethylene]-1-piperidinyl}ethyl}-7-methyl-5H-thiazolo(3,2-a)pyrimidine-5-one** Potentiates the activity of protein kinase C by inhibiting diacylglycerol metabolism. Inhibits diacylglycerol kinase (IC_{50} = 2.8 µM) without affecting phosphodiesterase or phosphatidylinositol kinase. Weak dopamine D_2 and histamine H_1 antagonist and strong serotonin S_2 antagonist.	5 mg
Diacylglycerol Kinase Inhibitor II	**266788**	**3-{2-[4-[*bis*-(4-Fluorophenyl)methylene]-1-piperidinyl]ethyl}-2,3-dihydro-2-thioxo-4(1H)quinazolinone** Inhibits diacylglycerol kinase in isolated platelet membranes (IC_{50} = 300 nM) and in intact platelets (IC_{50} = 120 nM) by binding to the catalytic domain. A more potent analog of diacylglycerol kinase inhibitor I (Cat. No.266785).	5 mg
RHC-80267	**554994**	**1,6-*bis*(Cyclohexyloximinocarbonylamino)hexane** Selective inhibitor of DAG lipase activity in canine platelets (IC_{50} = 4 nM) and in a variety of mammalian cells. Also inhibits glucose- and carbachol-induced insulin release from intact islets. An inhibitor of Angiotensin II (Cat. No.05-23-0101) and ATP-induced synthesis of 6-keto-prostaglandin F1α.	10 mg

Fatty Acid Amide Hydrolase Inhibitors

Product	Cat. No.	Comments	Size
FAAH Inhibitor I	**341248**	**4-Benzyloxyphenyl-n-butylcarbamate, Fatty Acid Amide Hydrolase Inhibitor I, URB532** A cell-permeable carbamate compound that acts as a potent, selective, and irreversible inhibitor of fatty acid amide hydrolase (FAAH; IC_{50} = 396 nM in brain membranes). Shown to block anandamide (Cat. No.172100) breakdown in cultured rat cortical neurons (IC_{50} = 214 nM) and inhibit brain FAAH activity (ID_{50} = 0.6 mg/kg) and modulate anxiety in rats. It does not affect the activities of serine hydrolases (IC_{50} > 30 µM), AChE (acetylcholinesterase), BCh (butyrylcholinesterase), and MGL (monoglyceride lipase). Does not show any interaction with several ion-channels, neurotransmitter transporters, or affect the ligand binding of cannabinoid receptors, CB1 and CB2 (IC_{50} > 300 µM).	10 mg
FAAH Inhibitor II	**341249**	**3'-Carbamoyl-biphenyl-3-yl-cyclohexylcarbamate; Cyclohexylcarbamic acid-3'-carbamoyl-biphenyl-3-yl Ester; URB597** A cell-permeable carbamate compound that acts as a potent, selective, and irreversible inhibitor of fatty acid amide hydrolase (FAAH; IC_{50} = 4.6 nM in brain membranes). Shown to block anandamide (Cat. No.172100) breakdown in rat cortical neurons (IC_{50} = 500 pM) and modulate anxiety in rats (ID_{50} = 0.15 mg/Kg). Does not affect the activities of several serine hydrolases (IC_{50} > 30 µM), including AChE (acetylcholinesterase), BCh (butyrylcholinesterase) and MGL (monoglyceride lipase). It also does not interfere with the binding of anandamide to cannabinoid receptors CB1 and CB2 (IC_{50} > 100 µM), as well as several ion-channels and neurotransmitter transporters.	5 mg

Fatty Acid Binding Inhibitors

Product	Cat. No.	Comments	Size
FABP4 Inhibitor	**341310**	**((2'-(5-Ethyl-3,4-diphenyl-1H-pyrazol-1-yl)(1,1'-biphenyl)-3-yl)oxy)-acetic acid** A cell-permeable biphenylazolo-oxyacetate that acts as a potent and selective inhibitor of adipocyte Fatty-Acid-Binding Protein (aFABP/aP2) by targeting its fatty acid-binding pocket (K_i = i = 250 nM and 350 nM, respectively). Shown to effectively block foam cell transformation and the cellular expression of inflammatory mediators in aP2-positive, but not aP2-negative, THP-1 macrophage *in vitro*, as well as improve the glucose metabolism and insulin sensitivity in mice *in vivo*.	5 mg

Fatty Acid Synthase Inhibitors

Product	Cat. No.	Comments	Size
Cerulenin, *Cephalosporium caerulens*	**219557**	**(2R, 3S)-2, 3-epoxy-4-oxo-7, 10-trans, trandocecadienamide** An antifungal antibiotic that inhibits sterol and fatty acid biosynthesis. In fatty acid synthesis, reported to bind in equimolar ratio to ß-keto-acyl-ACP synthase. In sterol synthesis, inhibits HMG-CoA synthetase activity. Also shown to inhibit feeding and induce dramatic weight loss in mice.	5 mg
Fatty Acid Synthase Inhibitor, C75	**341325**	**3-Carboxy-4-octyl-2-methylenebutyrolactone,** ***trans*****-4-Carboxy-5-octyl-3-methylenebutyrolactone** A cell-permeable α-methylene-γ-butyrolactone compound that potently inhibits FAS (fatty acid synthase) activity and stimulates CPT-1 (carnitine palmitoyltransferase-1), two key enzymes involved in the fatty acid biosynthesis. Acts centrally (reduces NPY expression) and peripherally (activates CPT-1 and fatty acid oxidation activity) to cause reduced food intake and body weight in mice. Promotes cell cycle arrest in human cancer cells culminating in apoptosis.	5 mg

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

HMG-CoA reductase catalyzes the 4-electron reduction of HMG-CoA to CoA and mevalonate, with oxidation of two molecules of NADPH. Regulation of the expression of hepatic 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 hypocholesterolemic 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.

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

Product	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 ß-keto-acyl-ACP synthase. In sterol synthesis, inhibits HMG-CoA synthetase activity. Also shown to inhibit feeding and induce dramatic weight loss in mice.	5 mg
Fluvastatin, Sodium Salt	**344095**	**{(±)-(3R',5S',6E)-7-[3-(4-Fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate, sodium}** A synthetic HMG-CoA reductase inhibitor (IC_{50} = 40-100 nM for human liver microsomes) that acts as an anti-hypercholesterolemic agent. Decreases the basal MMP-1 levels in culture media of endothelial cells in a time- and dose-dependent manner. Inhibits the formation of TBA-reactive substances in Fe(II)-supported peroxidation of liposomes (IC_{50} = 12 µM).	25 mg
Lovastatin	**438185**	**(Mevinolin; MK-803)** An anti-hypercholesterolemic agent that inhibits the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Has been shown to block a series of biological events including: the activation of $p21^{ras}$ by insulin in 3T3-L1 fibroblasts and 3T3-L1 adipocytes; the farnesylation of $p21^{ras}$, which decreases the pool of intracellular Ras available for subsequent activation by growth factors (including insulin); and N-*ras*-induced neuronal differentiation. Causes cell cycle arrest in the late G_1 phase through inhibition of proteasome. Has recently been shown to inhibit the stimulation of MAP kinase by insulin in HIRcB cells and to block the transcription of type-I SCR gene in THP-1-derived macrophages. Also blocks PDGF receptor tyrosine phosphorylation and MAP kinase activation by PDGF. This product requires activation for use in cell synchronization studies and in cell-free assay systems for HMG-CoA studies.	25 mg
Lovastatin, Sodium Salt	**438186**	Carboxylate form of Lovastatin (Cat. No.438185) that is active in whole cells and cell-free assays.	5 mg
Mevastatin	**474700**	**(Compactin)** An antibiotic that acts as a potent inhibitor of HMG-CoA reductase, thus suppressing Ras farnesylation. Inhibitor of myoblast fusion. Also may induce bone morphogenic protein-2 (BMP-2). Causes cell cycle arrest in late G_1 phase.	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**	**{(ßR,δR,1S,2S,6S,8S,8aR)-1,2,6,7,8,8a-Hexahydro-ß,δ,6-trihydroxy-2-methyl-8[(2S)-2-methyl-1-oxobutoxyl]-1-naphthaleneheptanoic Acid Na; 3ß-Hydroxycompactin, Na}** A water-soluble, competitive 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that potently blocks *in vivo* cholesterol synthesis (K_i = ~1 nM). Offers cardioprotection. Also acts as an immunomodulator and an inhibitor of ras p21 isoprenylation.	25 mg

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

Product	Cat. No.	Comments	Size
Simvastatin	**567020**	**(MK-733)** A lipophilic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor that blocks Ras function through inhibition of farnesylation. Also inhibits glucose-induced Ca^{2+} signaling and insulin secretion by blocking L-type Ca^{2+} channels in rat islet ß-cells. Inhibits cell proliferation of human smooth muscle cells. Note: this product is supplied in an inactive form and requires treatment with NaOH in EtOH followed by neutralization to pH 7.2 for activation.	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

IP3 Kinase Inhibitor

Product	Cat. No.	Comments	Size
IP3K Inhibitor	**406170**	A cell-permeable 2,6-disubstituted purine compound that acts as a selective, ATP-competitive inhibitor of IP 3-K (IC_{50} = 10.2 µM), the kinase that catalyzes the conversion of IP3 (Cat. Nos.407123 and407137) to IP4 (Cat. No.407126). Induces elevated cellular IP3 level and Ca^{2+}-release in a dose-dependent manner (5 to 20 µM in HL60 cells). Exhibits negligible inhibitory effect on Cdk1 (IC_{50} >100 µM) and two other IP3 metabolizing enzymes, PLC and IP3 5-ppase, even at concentrations as high as 200 µM. Useful alternative to the non-cell-permeable IP3 or IP3 analogs for studies involving intact cells.	5 mg

Lipase Inhibitors

Product	Cat. No.	Comments	Size
Lipase Inhibitor, THL	**437701**	**Orlistat** A cell-permeable, reactive, ß-lactone compound that promotes weight loss. Acts as a tight-binding, irreversible inhibitor of gastric and pancreatic lipases with minimal activity against amylase, trypsin, chymotrypsin, or phospholipase A_2. Covalently modifies a serine residue at the catalytic active site and partially inhibits the hydrolysis of triglycerides and lowers the absorption of dietary fat. Also reported to exhibit antitumor activity by inhibiting the thioesterase domain of fatty acid synthase both *in vitro* and *in vivo*.	50 mg
Monoacylglycerol Lipase Inhibitor, URB602	**475740**	A cell-permeable N-biphenyl carbamate compound that acts as a selective and non-competitive inhibitor of monoacylglycerol lipase (IC_{50} = 28 µM for rat brain MGL). Does not inhibit the activities of diacylglycerol lipase, FAAH, or COX-2. Shown to enhance stress-induced antinociception in rats, presumably by increasing the levels of 2-AG (arachidonyl glycerol).	10 mg

Lipoxygenase (LOX) Inhibitors

Lipoxygenases (LOX) belong to a heterogenous family of lipid-peroxidizing enzymes and are involved in the biosynthesis of mediators of inflammation. Based on their regiospecificity during interaction with substrates, 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. 15-LOX has also been implicated in the pathogenesis of altherosclerosis.

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Lipoxygenase (LOX) Inhibitors

Product	Cat. No.	Comments	Size
Acetyl-11-keto-ß- Boswellic Acid, *Boswellia serrata*	**110123**	**(3-O-Acetyl-11-keto-ß-Boswellic Acid; AKBA; AKßBA)** A cell-permeable pentacyclic triterpene of the ursane type that displays anti-tumor and anti-inflammatory properties. Shown to block the phosphorylation and degradation of IκBα and inhibit NF-κB-mediated gene transcription in chemoresistant, androgen-independent PC-3 prostate cancer cells (~10 µM). Mobilizes intracellular Ca^{2+} and stimulates the activation of p42/44 and p38 MAPKs (~30 µM in human PMN) and increases the formation of reactive oxygen species. Also reported to induce apoptosis and act as a non-redox, non-competitive inhibitor of 5-lipoxygenase (IC_{50} = 1.5 µM in rat PMNLs), and topoisomerase I (≥ 10 µM in calf thymus). When complexed with γ-cyclodextrin to facilitate its delivery, AKßBA has been demonstrated to exhibit *in vivo* efficacy in tumor growth and inhibition.	5 mg
Baicalein	**196322**	**(5,6,7-Trihydroxyflavone)** A cell-permeable flavone that inhibits the activity of 12-lipoxygenase (IC_{50} = 120 nM) and reverse transcriptase. Protects cortical neurons from ß-amyloid induced toxicity. Reduces leukotriene biosynthesis and inhibits the release of lysosomal enzymes. Also inhibits cellular Ca^{2+} uptake and mobilization, and adjuvant-induced arthritis. Reported to inhibit microsomal lipid peroxidation by forming an iron-baicalein complex. Inhibits topoisomerase II and induces cell death in hepatocellular carcinoma cell lines. Potentiates contractile responses to nerve stimulation. Inhibits protein tyrosine kinase and PMA-stimulated protein kinase C.	10 mg
Caffeic Acid	**205546**	A natural dietary compound reported to have anti-carcinogenic and anti-inflammatory properties. A cell-permeable, selective, non-competitive inhibitor of 5-lipoxygenase (ID_{50} = 3.7 µM). Inhibits Cu^{2+}-induced LDL oxidation in the initiation phase but acts as a prooxidant in the propagation phase. An irreversible inhibitor of glutathione S-transferases and a non-competitive inhibitor of xanthine oxidase.	500 mg

Lipoxygenase (LOX) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Curcumin, *Curcuma longa* L.	**239802**	**[1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]** A cell-permeable and irreversible antitumor and anti-inflammatory agent that acts as an inhibitor of 5-lipoxygenase (IC_{50} = 8 µM) and cyclooxygenase (IC_{50} = 52 µM). Confers significant protection against neurotoxic and genotoxic agents. Also inhibits the induction of nitric oxide synthase in activated macrophages (IC_{50} = 6 µM). Recently shown to inhibit the EGF receptor intrinsic kinase activity in the human epidermoid carcinoma A431 cells in a dose- and time-dependent manner. Also shown to be a p300/CREB-binding protein-specific inhibitor of histone acetyltransferase, inhibiting the acetylation of histones H3 and H4 with an IC_{50} of ~25 µM. Does not affect p300/CREB binding protein-associated factor (PCAF).	100 mg
Eicosapentaenoic Acid	**324875**	**(C20:5 ω-3; 5,8,11,14,17-Eicosapentaenoic Acid; EPA)** Cell permeable. Shown to have a beneficial effect in cardiovascular diseases and inflammation. Causes elevation of intracellular free Ca^{2+}. Inhibits 5-lipoxygenase and reduces thromboxane A_2 production and blood viscosity. Reported to induce apoptosis in pancreatic cancer cell lines and to inhibit liver metastasis.	25 mg
ETYA	**434741**	**(5,8,11,14-Eicosatetraynoic Acid)** Cell permeable. Inhibits arachidonic acid uptake and the activities of arachidonic acid specific and non-specific acyl-CoA synthetases. Inhibits phospholipase A_2 (PLA_2) and cytochrome P-450. Inhibits cyclooxygenase (ID_{50} = 8 µM), 5-lipoxygenase (ID_{50} = 10 µM), 12-lipoxygenase (ID_{50} = 300 nM), and 15-lipoxygenase (ID_{50} = 200 nM) in whole cells. Also acts as a potent modulator of Ca^{2+} entry into cells. Blocks monocyte binding in minimally-oxidized LDL in endothelial cells. Stimulates luteinizing hormone release from cultured pituitary cells.	20 mg
Ketoconazole	**420600**	**{cis-1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine; R-41400}** An inhibitor of cytochrome P-450 in steroid biosynthesis. An antifungal agent that displays potent anti-metastatic, anti-neoplastic, and anti-psoriatic activities. Also acts as an inhibitor of 5-lipoxygenase (5-LO; IC_{50} = 26 µM) and thromboxane synthase activities.	50 mg
MK-886	**475889**	**{3-[1-(*p*-Chlorobenzyl)-5-(isopropyl)-3-*t*-butylthioindol-2-yl]-2,2-dimethylpropanoic Acid, Na}** A cell-permeable, potent, and specific inhibitor of leukotriene biosynthesis (IC_{50} = 102 nM). Prevents the activation of 5-lipoxygenase by binding to 5-lipoxygenase-activating protein (FLAP); however, it does not affect 5-lipoxygenase activity in cell-free systems. Exhibits no effect on other pathways of arachidonic acid metabolism, including the cyclooxygenase, 12-lipoxygenase, and 15-lipoxygenase pathways.	5 mg
NDGA, Larrea divaricata	**479975**	**(Nordihydroguaiaretic Acid)** A cell-permeable antioxidant and a selective lipoxygenase (LOX) inhibitor (IC_{50} = 200 nM, 30 µM, and 30 µM for 5-LOX, 12-LOX, and 15-LOX, respectively) over cyclooxygenase (IC_{50} = 100 µM). Also shown to inhibit platelet-derived growth factor (PDGF)-stimulated DNA synthesis in Swiss/3T3 cells. A powerful hydroxy radical quencher.	250 mg
Ro106-9920	**557550**	A cell-permeable tetrazolopyridazine-phenylsulfoxide compound that displays anti-inflammatory properties. Acts as 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-1ß, and IL-6 inhibition) and rats. Does not inhibit $SCF^{\beta TRCP}$(IκBα ubiquitin ligase)-mediated ß-catenin ubiquitination in Jurkat cells. At 10 µM concentrations, also inhibits the activities of 5-lipoxygenase (by 89%) and EGFR kinase (by 63%).	1 mg 5 mg
SKF-86002	**567305**	**{6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridyl)imidazo[2,1-b]thiazole}** A cell-permeable, reversible, and ATP-competitive cytokine-suppressive anti-inflammatory drug (CSAID). A bicyclic imidazole that inhibits lipolysaccharide (LPS)-stimulated human monocyte IL-1 and TNF-α production (IC_{50} = 1 µM). Also acts as an inhibitor of both cyclooxygenase and 5-lipoxygenase. SKF-86002 also acts as a specific p38 MAP kinase inhibitor.	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 (IP_3). IP_3 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**	**(Arachidonyltrifluoromethyl Ketone)** A cell-permeable trifluoromethyl ketone analog of arachidonic acid. Potent and selective slow-binding inhibitor of cytosolic (85 kDa) phospholipase A_2 ($cPLA_2$; IC_{50} = ~20 µM). Specific inhibition of $cPLA_2$ activity by $AACOCF_3$ partially inhibits TNF-induced apoptosis without inhibition of caspase activity. Causes a significant diminution in thromboxane B_2 production in thrombin-stimulated platelets. Also inhibits platelet aggregation in response to collagen and arachidonic acid.	10 mg
ACA	**104550**	**[N-(*p*-Amylcinnamoyl)anthranilic Acid]** A cell-permeable inhibitor of phospholipase A_2 that blocks epinephrine-stimulated thromboxane production in platelets. Inhibits ATP-stimulated phosphatidylcholine (PC) secretion in alveolar type II cells. Also blocks phorbol ester and A23187-induced PC secretion in type II cells. Reported to block glucose-induced insulin secretion by pancreatic ß-cells. Exhibits moderate leukotriene antagonist activity.	25 mg
Aristolochic Acid	**182300**	A 1:1 mixture of aristolochic acids I and II. Phenanthrenecarboxylic acid derivative found in *Aristolochiaceae* that has been reported to inhibit phospholipase A_2 (PLA_2) from various snake venoms as well as human platelet and synovial fluid PLA_2. Inhibits ionophore-stimulated PLA_2 activity (IC_{50} = 40 µM) in human neutrophils. Exhibits greater inhibitory activity towards group II PLA_2 than group I PLA_2.	50 mg
cPLA2α Inhibitor	**525143**	**{N-{(2S,4R)-4-(Biphenyl-2-ylmethyl-isobutyl-amino)-1-[2-(2,4-difluorobenzoyl)-benzoyl]-pyrrolidin-2-ylmethyl}-3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-phenyl]acrylamide, HCl}** A cell-permeable 1,2,4-trisubstituted pyrrolidine derivative that acts as a highly specific and potent inhibitor of cPLA2α (cytosolic phospholipase A2α) (IC_{50} = 1.8 nM). Blocks the release of eicosanoids from A23187-stimulated THP-1 cells (IC_{50} = 22 nM for arachidonic acid, 31 nM for prostaglandin E2, 13 nM for leukotriene C4). Displays over 230-fold greater potency in the enzyme assay and ~ 3900-fold greater potency in the cellular assay than $AACOCF_3$ (Cat. No.100109). Does not exert any significant effects on the activities of cycloxygenase and 5-lipoxygenase.	500 µg
D-*erythro*-Sphingosine, Dihydro-	**300230**	**(Sphinganine)** Biosynthetic precursor of sphingosine. Inhibits protein kinase C (PKC) in Chinese hamster ovary cells (IC_{50} = 2.8 µM). Also directly inhibits phospholipase A_2 (PLA_2) and phospholipase D (PLD).	10 mg
D609, Potassium Salt	**251400**	**(Tricyclodecan-9-yl-xanthogenate, K)** Selective inhibitor of phosphatidylcholine (PC)-specific phospholipase C (K_i = 5-10 µM). Does not inhibit phosphatidylinositol-specific phospholipase C, phospholipase A, or phospholipase D. Also reported to inhibit LPS-stimulated ERK activation via its inhibitory effect on PLC. Inhibits angiogenesis by preventing the synthesis of basement membrane.	5 mg

Phospholipase Inhibitors *continued*

Product	Cat. No.	Comments	Size
ET-18-OCH_3	**341207**	**(Edelfosine; 1-O-Octadecyl-2-O-methyl-*rac*-glycero-3-phosphorylcholine)** A cell-permeable and reversible cytotoxic agent that shows selective cytocidal activity against neoplastic cells and virally transformed cells. Selectively inhibits phosphatidylinositol-specific phospholipase C (PI-PLC; IC_{50} = 15 µM) but does not inhibit phosphatidylcholine-specific PLC or PLD. Promotes apoptosis in mitogen-activated, but not resting, T lymphocytes in a dose- and time-dependent manner. Also promotes rapid and selective apoptosis in human leukemic cells.	5 mg
HELSS	**374085**	**BEL, E-6-(Bromomethylene)tetrahydro-3-(1-naphthalenyl)-2H-pyran-2-one, Haloenol lactone suicide substrate** A potent, cell-permeable, and irreversible inhibitor of calcium-independent phospholipase A_2 (PLA_2; IC_{50} = 60 nM). Exhibits 1000-fold higher selectivity for calcium-independent PLA_2 versus calcium-dependent PLA_2. Inhibits the release of prostaglandin E_2 and suppresses glucose-stimulated release of insulin from pancreatic ß cells.	5 mg
Isotetrandrine	**419650**	A biscoclaurine alkaloid that inhibits G-protein activation of phospholipase A_2 but not phospholipase C or phospholipase D.	1 mg
Methyl Arachidonyl Fluorophosphonate	**454565**	**(MAFP)** A selective, active site-directed, irreversible inhibitor of both calcium-dependent and calcium-independent cytosolic (85 kDa) phospholipase A_2 (PLA_2) but not of secretory PLA_2.	1 mg
MJ33	**475865**	**[1-Hexadecyl-3-(trifluoroethyl)-*sn*-glycero-2-phosphomethanol, Li]** A novel active site-directed, specific, competitive, and reversible inhibitor of phospholipase A_2 (PLA_2). Shows high specificity for type I (pancreatic) and bee venom PLA_2 but has relatively poor affinity for type II human synovial PLA_2. MJ33 has inhibitory activity against a low pH calcium-independent PLA_2 as well as against the PLA_2 activity responsible for permeability barrier homeostasis or esophagitis.	5 mg
Neomycin Sulfate	**4801**	An aminoglycoside antibiotic that inhibits translation by binding to the small subunit of prokaryotic ribosomes. Recently shown to inhibit angiogenin-induced angiogenesis. Blocks voltage-sensitive Ca^{2+} channels without affecting Na^+ - Ca^{2+} antiporter in nerve cells. A potent inhibitor of skeletal muscle sarcoplasmic reticulum Ca^{2+} release. An inhibitor of inositol phospholipid turnover. A non-specific phospholipase C inhibitor. Also inhibits phosphatidylcholine-phospholipase D activity (IC_{50} = 65 µM). Inhibits angiogenin-induced angiogenesis in the chicken chorioallantoic membrane (20 ng per egg).	25 g
Neomycin Sulfate, γ-Irradiated, Tissue Culture Grade	**480100**	Sterilized by γ-irradiation. An aminoglycoside antibiotic that inhibits translation by binding to the 30S ribosomal subunit.	20 ml
$PACOCF_3$	**506274**	**(Palmitoyl Trifluoromethyl Ketone)** A novel Ca^{2+}-independent and reversible inhibitor of phospholipase A_2 (PLA_2; IC_{50} = 3.8 µM). May also inhibit Ca^{2+}-dependent PLA_2 at much higher concentrations (IC_{50} = 45 µM).	5 mg
Quercetin, Dihydrate	**551600**	**(3,3',4',5,7-Pentahydroxyflavone)** A cell-permeable and reversible inhibitor of PIM1 kinase (IC_{50} = 43 nM), PI 3-K (IC_{50} = 3.8 µM) and phospholipase A_2 (IC_{50} = 2 µM). Also inhibits mitochondrial ATPase, phosphodiesterases, and protein kinase C. Induces apoptosis in K562, Molt-4, Raji, and MCAS tumor cell lines. Reported to activate sirtuins and promote the survival of eukaryotic cells.	100 mg
Quinacrine, Dihydrochloride	**551850**	**(Mepacrine)** A non-specific phospholipase A_2 (PLA_2) inhibitor. Acts as an acetylcholine receptor antagonist. Suppresses glibenclamide-sensitive K^+-currents (IC_{50} = 4.4 µM). Also inhibits monoamine oxidase (MAO).	100 mg
Spermine, Tetrahydrochloride	**5677**	Polyamine that plays an important role in the regulation of cellular proliferation and differentiation. Has both stimulatory and inhibitory effects on NMDA receptors depending on the subunit composition of the receptor. Acts as an inhibitor of phospholipase Cα and an activator of phospholipase Cδ. Inhibits DNA fragmentation and morphological apoptosis. Inhibits neuronal NOS.	5 g
sPLA2-IIA Inhibitor I	**525145**	**[c(2NapA)LS(2NapA)R, TFA]** A highly hydrophobic cyclic pentapeptide that selectively binds and acts as a potent inhibitor of $sPLA_2$-IIA (human type IIA secreted phospholipase A_2; IC_{50} = 12.8 µM). Shown 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 have any significant effect on the activities of porcine $sPLA_2$-IB, *Naja naja* $sPLA_2$-IB, or *Crotalus durissus* $sPLA_2$-IIA even at 10 µM concentration.	1 mg
ST638	**567790**	**[α-Cyano-(3-ethoxy-4-hydroxy-5-phenylthiomethyl)cinnamide]** A cell-permeable, reversible, and substrate competitive protein tyrosine kinase inhibitor (IC_{50} = 370 nM) that also inhibits HGF-induced MAP kinase activation in hepatocytes. Also shown to inhibit phospholipase D activity in human neutrophils. Decreases the O_2^- production induced by pervanadate in guinea pig neutrophils.	5 mg

Phospholipase Inhibitors *continued*

Product	Cat. No.	Comments	Size
U-73122	**662035**	**{1-[6-((17ß-3-Methoxyestra-1,3,5(10)-trien-17-yl) amino)hexyl]-1H-pyrrole-2,5-dione}** Inhibits agonist-induced phospholipase C activation (IC_{50} = 1-2.1 µM) in human platelets and neutrophils. Inhibits ET-1 and parathyroid hormone-induced Ca^{2+} transients (IC_{50} = 800 nM and 500 nM, respectively). Also inhibits agonist-induced down-regulation of muscarinic receptors in SK-N-SH neuroblastoma cells. Acts as a potent inhibitor of human polymorphonuclear neutrophil adhesion on biological surfaces (IC_{50} = 50 nM). Reported to abolish T lymphoma cell invasion into fibroblast monolayers.	5 mg
U-73343	**662041**	**{1-[6-((17ß-3-Methoxyestra-1,3,5(10)-trien-17-yl) amino)hexyl]-2,5-pyrrolidinedione}** A cell-permeable analog of U-73122 (Cat. No.662035) that acts as a very weak inhibitor of phospholipase C. 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, which results in progressive enlargement of liver and spleen.

References:

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Sphingomyelinase Inhibitors

Product	Cat. No.	Comments	Size
Chlorpromazine, Hydrochloride	**215921**	**{2-Chloro-10-[3'-(dimethylamino)propyl]phenothiazine, HCl}** Inhibits calmodulin-dependent stimulation of cyclic nucleotide phosphodiesterase (IC_{50} = 17 µM). Acts as a peripheral vasodilator. Acts as an inhibitor of lysosomal sphingomyelinase and of TNF-α production. Inhibits nitric oxide synthase (NOS) in mouse brain and prevents lipopolysaccharide induction of NOS in murine lung. Shown to potently and specifically inhibit KSP/Eg5 (IC_{50} < 10 µM), and PLA2.	500 mg
3,4-Dichloroisocoumarin	**287815**	A potent, irreversible inhibitor of serine proteases. Reacts with serine proteases to release an acylchloride moiety that can acylate another active site residue. Inhibits granzyme B and blocks apoptotic internucleosomal DNA cleavage in thymocytes without the involvement of endonucleases. Does not affect thiol proteases and metalloproteases. Does not exhibit any activity towards ß-lactamases.	10 mg
Fumonisin B_1, *Fusarium moniliforme*	**344850**	**(FB_1)** A cell-permeable mycotoxin that inhibits sphingolipid biosynthesis in rat kidney and in liver microsomes by inhibition of sphingosine N-acyltransferase (ceramide synthase; IC_{50} = 100 nM). Preferentially inhibits sphingomyelin biosynthesis in neuronal cells. Exhibits carcinogenic properties.	1 mg

Sphingomyelinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Gentamycin Sulfate	**345814**	Broad-spectrum cell culture antibiotic that is nontoxic to viruses and mammalian cells at antibacterial and antimycoplasmal concentrations. Its extended stability and slow development of bacterial resistance allow long-term virus and tissue culture studies. Composed of three closely related components: gentamycin C_1, C_{1a}, and C_2. Reduces sphingomyelinase activity in fibroblasts. M.W. refers to C_2 free base form.	1 g
Manumycin A, *Streptomyces parvulus*	**444170**	An antibiotic with antitumor properties. A cell-permeable potent and selective inhibitor of farnesyltransferase (FTase; IC_{50} = 5 µM) compared to geranylgeranyltransferase I (GGTase I; IC_{50} = 180 µM). Manumycin acts as a competitive inhibitor of FTase with respect to farnesylpyrophosphate (FPP; K_i = 1.2 µM), but acts as a noncompetitive inhibitor with respect to the Ras acceptor protein. Reported to inhibit the growth and invasive activity of pancreatic cancer cells.	1 mg
N-SMase Inhibitor, GW4869	**567715**	**(GW554869A; GW69A; Sphingomyelinase, Neutral, Inhibitor GW4869)** A cell-permeable, symmetrical dihydroimidazolo-amide compound that acts as a potent, specific, non-competitive inhibitor of N-SMase (neutral sphingomyelinase) [IC_{50} = ~ 1 µM, rat brain; K_m for sphingomyelin ~13 µM]. Does not inhibit human A-SMase (acid sphingomyelinase) even at 150 µM. Weakly inhibits the activities of bovine protein phosphatase 2A and mammalian lyso-PAF PLC, while no inhibition is observed for bacterial phosphatidylcholine-specific PLC. Reported to offer complete protection against TNF-α or diamine-induced cell death in MCF7 breast cancer cells at 20 µM. Does not modify the intracellular glutathione levels or interfere with TNF-α or diamine-mediated signaling effects.	1 mg
N^a-Tosyl-Phe Chloromethyl Ketone	**616387**	**(TPCK)** Irreversible inhibitor of chymotrypsin. Useful for inhibiting chymotrypsin activity in trypsin preparations. Inhibits apoptosis in thymocytes. Blocks the induction of nitric oxide synthase by γ-interferon and lipopolysaccharides (EC_{50} = 20 µM).	250 mg 1 g

Sphingosine Kinase Inhibitors

Product	Cat. No.	Comments	Size
D-*erythro*-Sphingosine, N,N-Dimethyl-	**310500**	A cell-permeable and reversible inhibitor of protein kinase C (PKC; IC_{50} = 12 µM) and stimulates Src kinase activity. Useful for inhibiting cell surface expression of selectins that promote adhesion of leukocytes or tumor cells to platelets and endothelial cells. Induces apoptosis in human leukemia HL-60 cells. An inhibitor of sphingosine kinase.	5 mg
Sphingosine Kinase Inhibitor	**567731**	**[2-(*p*-Hydroxyanilino)-4-(*p*-chlorophenyl) thiazole; SK Inhibitor]** A cell-permeable disubstituted thiazole compound that displays anti-tumor properties. Acts as a potent, substrate competitive, reversible, and highly specific inhibitor of sphingosine kinase (IC_{50} = 0.5 µM for GST-hSK). Does not affect the kinase activity of hERK2, hPI3K, or PKCα even at concentrations as high as 60 µM. Induces apoptosis in human cancer cells that express the drug transport proteins Pgp or MRP1 (IC_{50} = ~ 1-5 µM) through inhibiting sphingosine-1-phosphate production.	10 mg

Squalene-2,3-oxide Cyclase Inhibitor

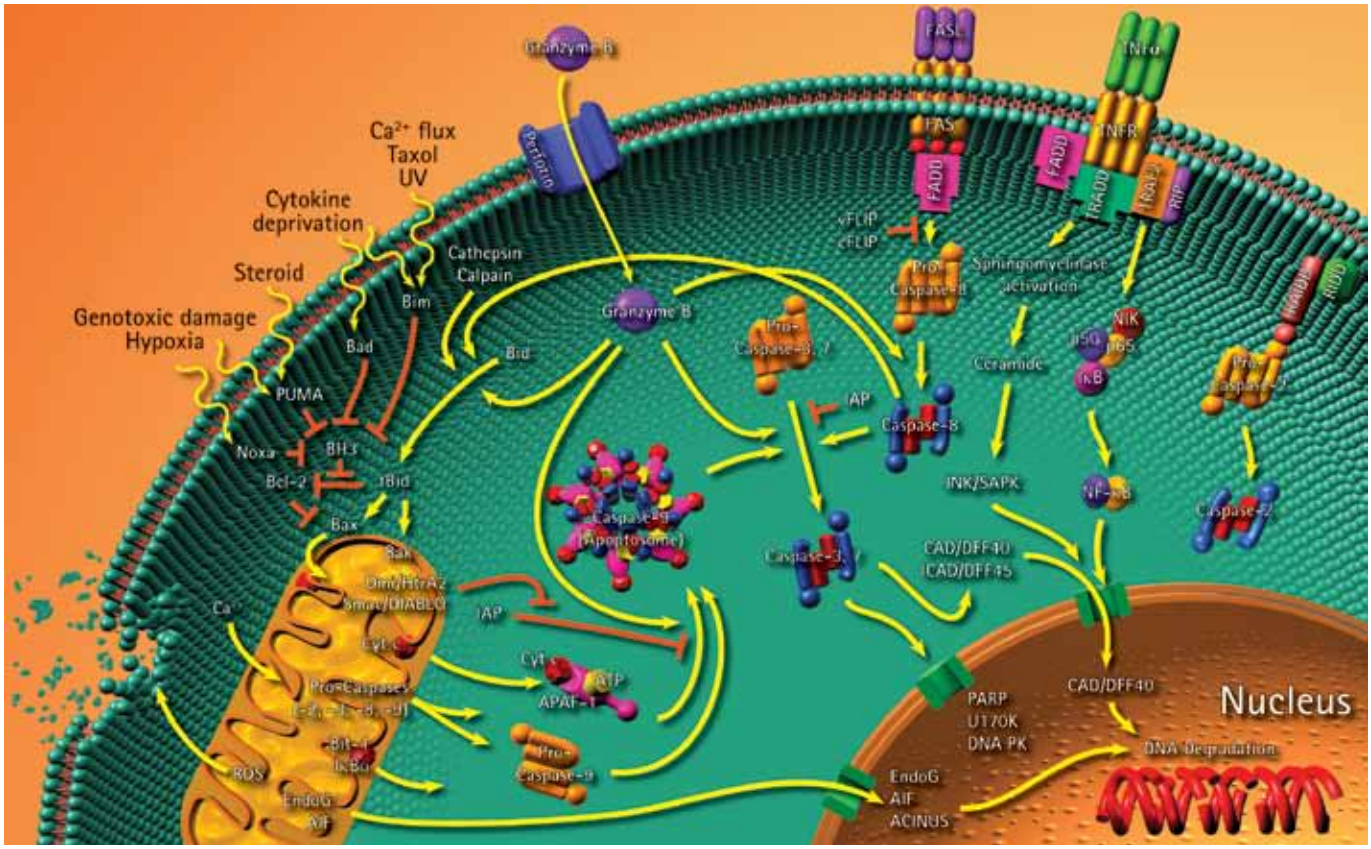
Product	Cat. No.	Comments	Size
AMO 1618	**1712**	Anticholesterolemic agent that can be used as an inhibitor of squalene-2,3-oxide cyclase to study the action of squalene epoxidase in the microsomal cholesterol biosynthetic pathway.	250 mg

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 by limited proteolysis, initiate the death program by destroying key components of the cellular infrastructure and activating factors that mediate damage to the cells. The mechanism of caspase activation appears to be conserved in evolution. 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 by two major pathways: the receptor-mediated (Fas ligand or TNF-α-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 inhibitors of caspases-1 ($K_i \approx 10$ nM), and exhibit very weak inhibitory effect on caspases-3 and -7 ($K_i \approx 50$ 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.



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Caspase Inhibitors

Product	Cat. No.	Comments	Size
InSolution™Caspase Inhibitor I	**627609**	When using with a purified recombinant enzyme, pretreatment with an esterase is required.	1 mg
Caspase Inhibitor I	**627610**	**Z-VAD (OMe)-FMK** A cell-permeable, irreversible, pan-caspase inhibitor. Inhibits Fas-mediated apoptosis in Jurkat cells and staurosporine-induced cell death in corneal epithelial cells. When using with purified native or recombinant enzyme, pre-treatment with an esterase is required.	1 mg
Caspase Inhibitor I, Biotin Conjugate	**218742**	**Biotin-X-VAD-FMK** Biotinylated derivative of Caspase Inhibitor I (Cat. No.627610) that may be used to identify active caspases in cell lysates.	1 mg
Caspase Inhibitor II	**218735**	**Ac-VAD-CHO** A potent and reversible pan-caspase inhibitor.	1 mg
Caspase Inhibitor II, Cell-Permeable	**218830**	**cpm-VAD-CHO; sequence** A cell-permeable, reversible pan-caspase inhibitor produced by attaching the N-terminal sequence (amino acids 1-16) of the Kaposi fibroblast growth factor signaling peptide, which imparts cell-permeability to VAD peptide.	1 mg
Caspase Inhibitor III	**218745**	**Boc-D-FMK** A cell-permeable, irreversible, broad-spectrum caspase inhibitor.	250 µg 1 mg
Caspase Inhibitor Set I	**235429**	Contains 1 mg of Caspase-3 Inhibitor II, Z-DEVD-FMK (Cat. No.264155); 1 mg of Caspase-1 Inhibitor I, Ac-YVAD-CHO (Cat. No.400010); and 1 mg of Caspase Inhibitor I, Z-VAD-FMK (Cat. No.627610). Supplied with a data sheet.	1 set
Caspase Inhibitor Set II	**218772**	**Solid. PROTECT FROM MOISTURE. A set of eight cell-permeable, irreversible inhibitors of various caspase-family proteases. Contains 250 µg 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 III, Boc-D-FMK (Cat. No. 218745). Supplied with a data sheet.** A set of eight cell-permeable, irreversible inhibitors of various caspase-family proteases. Contains 250 µg 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 III, Boc-D-FMK (Cat. No.218745). Supplied with a data sheet.	1 set
Caspase Inhibitor Set III	**218806**	A set of eight ready to use cell-permeable, irreversible inhibitors of various 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). Supplied with a data sheet.	1 set
Caspase Inhibitor Set IV	**218825**	A set of four ready-to-use cell-permeable, irreversible inhibitors of various caspase-family proteases and a negative control apoptosis inducer. Each vial 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. No218761); general caspase inhibitor, Z-VAD-FMK (Cat. No.627610); the negative control Z-FA-FMK (Cat. No.642000), and an aqueous solution (100 µl, 6.1 µg/µl) of an apoptosis inducer, Doxorubicin, Hydrochloride (Cat. No.324380). Supplied with a data sheet.	1 set
Caspase Inhibitor VI	**219007**	**Z-VAD-FMK** An irreversible general caspase inhibitor. Useful for studies involving recombinant, isolated, and purified caspase enzymes. Unlike Caspase Inhibitor I (Cat. No.627610), this inhibitor does not require pretreatment with esterase for *in vitro* studies. A 10 mM (1 mg/221 µl) solution of Caspase Inhibitor VI (Cat. No. 219011) in DMSO is also available.	250 µg
InSolution™Caspase Inhibitor VI	**219011**	A 10 mM (1 mg/221 µl) solution of Caspase Inhibitor VI (Cat. No. 219007) in DMSO.	1 mg
Caspase Inhibitor VIII	**218729**	**Ac-VDVAD-CHO** A potent, reversible inhibitor of caspase-2 (K_i = 3.5 nM), caspase-3 (K_i = 1 nM) and caspase-7 (K_i = 7.5 nM). Also serves as an inhibitor of DRONC (*Drosophila* caspase), a glutamate/aspartate protease.	1 mg

Caspase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Caspase Inhibitor X	**218723**	A benzodioxane containing 2,4-disubstituted thiazolo compound that acts as a selective, reversible and competitive inhibitor of caspases (K_i = 4.3 µM, 6.2 µM and 2.7 µM for caspase-3, -7 and -8, respectively). The benzodioxane moiety is shown to fit in the 'aspartate hole' of the caspases and possibly disrupt caspase-8 assisted cleavage of BID, a proapoptotic protein. Weakly affects the activity of anthrax lethal factor, a metalloprotease, at ~20 µM.	5 mg
Caspase-1 Inhibitor I	**400010**	**IL-1ß Converting Enzyme (ICE) Inhibitor I** A potent, specific, and reversible inhibitor of caspase-1 (K_i = 200 pM for human recombinant caspase-1), caspase-4, and caspase-5. Strongly inhibits anti-APO-1 induced apoptosis in L929-APO-1 cells.	1 mg 5 mg
Caspase-1 Inhibitor I, Cell-Permeable	**400011**	**Ac-AAVALLPAVLLALLAPYVAD-CHO** A cell-permeable inhibitor of caspase-1 (ICE; Interleukin-1ß Converting Enzyme), caspase-4, and caspase-5. The C-terminal YVAD-CHO sequence of this peptide is a highly specific, potent, and reversible inhibitor of caspase-1 (K_i = 1 nM). The N-terminal sequence (amino acid residues 1-16) corresponds to the hydrophobic region (h-region) of the signal peptide of the Kaposi fibroblast growth factor (K-FGF) and confers cell-permeability to the peptide.	1 mg
Caspase-1 Inhibitor II	**400012**	**IL-ß Converting Enzyme (ICE) Inhibitor II** A cell-permeable and irreversible inhibitor of caspase-1 (K_i = 760 pM), caspase-4, and caspase-5. Inhibits Fas-mediated apoptosis and acidic sphingomyelinase activation.	5 mg
Caspase-1 Inhibitor II, Biotin Conjugate	**400022**	**IL-1ß Converting Enzyme (ICE) Inhibitor II, Biotinylated** Biotinylated derivative of Caspase-1 Inhibitor II (Cat. No.400012) that can be used to label the caspase-1, caspase-4, and caspase-5 enzymes. Useful for the isolation, identification, and characterization of caspase-1 and caspase-4.	5 mg
Caspase-1 Inhibitor IV	**400015**	**Ac-YVAD-AOM** A highly selective, competitive, cell-permeable, and irreversible inhibitor of caspase-1, caspase-4, and caspase-5. Inactivates the enzyme with a rate limited by diffusion and is relatively inert toward other bionucleophiles such as glutathione, making it an excellent candidate for *in vivo* studies of enzyme inhibition.	1 mg
Caspase-1 Inhibitor V	**400019**	**Z-Asp-[(2,6-dichlorobenzoyl)oxy]methane** A potent inhibitor of caspase-1-like proteases. Blocks apoptotic cell death in human myeloid leukemia U937 cells and blocks etoposide-induced DNA fragmentation.	5 mg
Caspase-1 Inhibitor VI	**218746**	**Z-YVAD-FMK** A potent, cell-permeable, and irreversible inhibitor of caspase-1 (ICE), caspase-4, and caspase-5.	250 µg
Caspase-13 Inhibitor II	**219009**	**Z-LE(OMe)E(OMe)D(OMe)-FMK** A cell-permeable, irreversible inhibitor of caspase-13. When using with purified native or recombinant enzyme, pretreatment with an esterase is required.	250 µg
Caspase-2 Inhibitor I	**218744**	**Z-VD(OMe)VAD(OMe)-FMK** A cell-permeable and irreversible inhibitor of caspase-2 (ICH-1)	250 µg
Caspase-3 Inhibitor I	**235420**	**Ac-DEVD-CHO** A very potent, specific, and reversible inhibitor of caspase-3 (IC_{50} = 200 pM), caspase-6, caspase-7, caspase-8, and caspase-10.	1 mg 5 mg
Caspase-3 Inhibitor I, Biotin Conjugate	**235422**	**Biotin-DEVD-CHO** Affinity ligand for caspase-3, caspase-6, caspase-7, caspase-8, and caspase-10. Inhibits caspase-3 (IC_{50} = 200 pM) with similar potency to the parent compound (Cat. No.235420).	1 mg
Caspase-3 Inhibitor I, Cell-Permeable	**235423**	**Cell-permeable, DEVD-CHO** A cell-permeable inhibitor of caspase-3, as well as caspase-6, caspase-7, caspase-8, and caspase-10. The C-terminal DEVD-CHO sequence of this peptide is a highly specific, potent, and reversible inhibitor of caspase-3 (K_i 50 = 200 pM). The N-terminal sequence (amino acid residues 1-16) corresponds to the hydrophobic region (h-region) of the signal peptide of Kaposi fibroblast growth factor (K-FGF) and confers cell-permeability to the peptide. A 5 mM (1 mg/100 µl) solution of Caspase-3 Inhibitor I, Cell-permeable (Cat. No.235427) in DMSO is also available.	1 mg
InSolution™Caspase-3 Inhibitor I, Cell-Permeable	**235427**	**Cell-permeable, DEVD-CHO; CPP32/Apopain Inhibitor, Cell-permeable** A 5 mM (1 mg/100 µl) solution of Caspase-3 Inhibitor I, Cell-permeable (Cat. No. 235423) in DMSO.	1 mg
Caspase-3 Inhibitor II	**264155**	**Z-D(OMe)E(Ome)VD(OMe)-FMK** A potent, cell-permeable, and irreversible inhibitor of caspase-3 as well as caspase-6, caspase-7, caspase-8, and caspase-10. When using with purified native or recombinant enzyme, pretreatment with an esterase is required. A 5 mM (250 µg/75 µl) solution of Z-DEVD-FMK (Cat. No.264156) in DMSO is also available.	250 µg
InSolution™Caspase-3 Inhibitor II	**264156**	**Z-D(OMe)E(Ome)VD(OMe)-FMK** A 5 mM (250 µg/75 µl) solution of Z-DEVD-FMK (Cat. No. 264155) in DMSO.	250 µg

Caspase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Caspase-3 Inhibitor III	**218750**	**Ac-DEVD-CMK** A potent, cell-permeable, and irreversible inhibitor of caspase-3 as well as caspase-6, caspase-7, caspase-8, and caspase-10.	1 mg 5 mg
Caspase-3 Inhibitor IV	**235421**	**Ac-DMQD-CHO** A specific inhibitor of caspase-3. This tetrapeptide inhibitor has been used with the caspase-6 inhibitor Ac-VEID-CHO to dissect the pathway of caspase activation in Fas-stimulated Jurkat cells.	1 mg 5 mg
Caspase-3 Inhibitor V	**219002**	**Z-D(OMe)QMD(OMe)-FMK** A potent, cell-permeable, and irreversible inhibitor of caspase-3, also recognizes caspase-1. When using with purified native or recombinant enzyme, pre-treatment with an esterase is required.	1 mg
Caspase-3 Inhibitor VII	**219012**	**2-(4-Methyl-8-(morpholin-4-ylsulfonyl)-1,3-dioxo-1,3-dihydro-2H-pyrrolo[3,4-c]quinolin-2-yl)ethyl acetate** A cell-permeable, non-peptidyl pyrroloquinoline compound that acts as a potent, reversible, and non-competitive inhibitor of caspase-3 (IC_{50} = 23 nM) with 10-100-fold greater selectivity. Shown to display higher anti-apoptotic activity than Z-VAD-FMK (Cat. No.627610) in a model of Staurosporine- (Cat. No.569397) induced apoptosis in human Jurkat T cells.	1 mg
Caspase-3 Inhibitor VIII	**219013**	**N-Benzyloxycarbonyl-(S)-*tert*-butyl-Leu-Asp-Aldehyde** A cell-permeable dipeptidyl aspartic aldehyde that potently inhibits caspase-3 activity (Ki^0 = 3.6 nM) in a reversible and substrate-competitive manner. Z-tLeu-Asp-H, at a concentration of ≥0.43 nM, is shown to completely inhibit the vitamine E-induced PARP cleavage in human DLD-1 colon adenocarcinoma cells, while the activation of caspase-3 by its upstream caspases is not affected.	10 mg
Caspase-3/7 Inhibitor I	**218826**	**5-[(S)-(+)-2-(Methoxymethyl)pyrrolidino]sulfonylisatin** A potent, cell-permeable, and specific, reversible inhibitor of caspase-3 (K_i = 60 nM) and caspase-7 (K_i = 170 nM).	1 mg
Caspase-3/7 Inhibitor II	**218832**	**Ac-DNLD-CHO** A tetrapeptidyl aldehyde that acts as a potent, reversible and active site binding inhibitor of caspases-3 and -7 (IC_{50} = 3.2 nM and 22.6 nM, respectively) and displays ~100-fold greater selectivity over caspases-8 and -9 (IC_{50} = 577.6 nM and 364.7 nM, respectively). Offers protection against Camptothecin (Cat. No.208925), and anti-Fas-mediated apoptosis in Jurkat T cells.	1 mg
Caspase-4 Inhibitor I	**218755**	**Ac-LEVD-CHO** A reversible caspase-4 inhibitor.	1 mg
Caspase-4 Inhibitor I, Cell-Permeable	**218766**	**LEVD-CHO, Cell-permeable; sequence** A potent, cell-permeable, and reversible inhibitor of caspase-4. The N-terminal sequence (amino acid residues 1-16) corresponds to the hydrophobic region of the signal peptide of Kaposi fibroblast growth factor and confers cell permeability to the peptide.	1 mg
Caspase-5 Inhibitor I	**218753**	**Z-WE(OMe)HD(OMe)-FMK** A potent, cell-permeable, and irreversible inhibitor of caspase-5. Strongly inhibits caspase-1. Also inhibits caspase-4 and caspase-8.	250 µg
Caspase-6 Inhibitor I	**218757**	**Z-VE(OMe)ID(OMe)-FMK** A cell-permeable, irreversible inhibitor of caspase-6. When using with purified native or recombinant enzyme, pretreatment with an esterase is required.	250 µg
Caspase-6 Inhibitor II, Cell-Permeable	**218767**	**VEID-CHO, Cell-permeable; sequence** A potent, cell-permeable, and reversible inhibitor of caspase-6.The N-terminal sequence (amino acids 1-16) corresponds to the hydrophobic region of the signal peptide of Kaposi fibroblast growth factor and confers cell permeability to the peptide.	1 mg
Caspase-9 Inhibitor I	**218761**	**Z-LE(OMe)HD(OMe)-FMK** A potent, cell-permeable, and irreversible inhibitor of caspase-9. May also inhibit caspase-4 and caspase-5. When using with purified native or recombinant enzyme, pretreatment with an esterase is required. A 5 mM (250 µg/72 µl) solution of Z-LEHD-FMK (Cat. No.218841) in DMSO is also available.	250 µg
InSolution™Caspase-9 Inhibitor I	**218841**	**Z-LE(OMe)HD(OMe)-FMK** A 5 mM solution of Z-LEHD-FMK (Cat. No. 218761) in DMSO.	250 µg
Caspase-9 Inhibitor II, Cell-Permeable	**218776**	**LEHD-CHO, Cell-permeable** A potent, cell-permeable, and reversible inhibitor of caspase-9. May also inhibit caspase-4 and caspase-5. The N-terminal sequence (amino acids 1-16) corresponds to the hydrophobic region of the signal peptide of Kaposi fibroblast growth factor and confers cell permeability to the peptide.	1 mg
Caspase-9 Inhibitor III	**218728**	**Ac-LEHD-CMK** A potent, irreversible inhibitor of caspase-9. Reported to reduce myocardial infarct size during reperfusion (~70 nM).	1 mg

Caspase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Group III Caspase Inhibitor I	**368620**	**Z-AE(OMe)VD(OMe)-FMK** A potent, cell-permeable, and irreversible inhibitor of Group III caspases (caspase-6, -8, -9, and -10), although more effective towards caspases-6 and -8. Also inhibits caspase-1 and caspase-3. When using with purified native or recombinant enzyme, pretreatment with an esterase is required.	1 mg
InSolution™Q-VD-OPh, Non-O-methylated	**551476**	**N-(2-Quinolyl)valyl-aspartyl-(2,6-difluorophenoxy)methyl Ketone** A cell-permeable, irreversible, broad-spectrum caspase inhibitor (IC_{50} = 50, 100, 430, and <25 nM for caspase-1,-8, -9, and -3, respectively) with effective antiapoptotic properties against all major caspase-mediated cellular apoptosis pathways. Exhibits no cytotoxic effects even at extremely high concentrations.	1 mg

Granzyme Inhibitors

Product	Cat. No.	Comments	Size
Caspase-8 Inhibitor I, Cell-Permeable	**218773**	**(granzyme B Inhibitor II, Cell-permeable; IETD-CHO, Cell-permeable)** A potent, cell-permeable, and reversible inhibitor of caspase-8 and Granzyme B. The N-terminal sequence (amino acids 1-16) corresponds to the hydrophobic region of the signal peptide of Kaposi fibroblast growth factor and confers cell permeability to the peptide.	1 mg
Caspase-8 Inhibitor II	**218759**	**[granzyme B Inhibitor III; Z-IE(OMe)TD(OMe)-FMK]** A potent, cell-permeable, and irreversible inhibitor of caspase-8 and granzyme B. Effectively inhibits influenza virus-induced apoptosis in HeLa cells. Also inhibits granzyme B. When using with purified native or recombinant enzyme, pretreatment with an esterase is required. A 5 mM (250 µg/76 µl) solution of Z-IETD-FMK (Cat. No.218840) in DMSO is also available.	250 µg 1 mg
InSolution™Caspase-8 Inhibitor II	**218840**	**[granzyme B Inhibitor III; Z-IE(OMe)TD(OMe)-FMK]** A 5 mM (250 µg/76 µl) solution of caspase-8 Inhibitor II (Cat. No. 218759) in anhydrous DMSO.	250 µg
CrmA, Recombinant	**PF122**	CrmA (cowpox viral serpin cytokine response modifier A) is purified from *E. coli* transformed with a construct containing the full-length coding region of the CrmA gene and 7 additional amino acids that do not affect the activity. CrmA is a natural inhibitor of human caspase-1 and granzyme B, enzymes that are involved in apoptosis.	100 µg
Granzyme B Inhibitor I	**368050**	**(Z-AAD-CMK)** 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 (K_i = 1 nM). Also inhibits caspase-1 (<6 nM), caspase-6 (5.6 nM), and caspase-10 (27 nM).	1 mg
Granzyme B Inhibitor IV	**368056**	A reversible inhibitor of granzyme B and caspase-8.	1 mg

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Necrosis Inhibitors

Product	Cat. No.	Comments	Size
Necrosis Inhibitor, IM-54	**480060**	**2-(1H-Indol-3-yl)-3-pentylamino-maleimide** A cell-permeable mono-indolylmaleimide compound that selectively blocks oxidative stress-induced necrotic cell death (~3 µM IM-54 prevented ~50% cell death in HL60 cells exposed to 100 µM H_2O_2). Does not offer protection against Etoposide- (Cat. No.341205) induced apoptosis or display antioxidant properties. Does not affect the kinase activities of S6K1 and PKC isozymes even at concentrations as high as 50 µM.	5 mg
Necrostatin-1	**480065**	A cell-permeable, potent, and selective blocker of necroptosis (EC_{50} = 494 nM in FADD-deficient Jurkat cells treated with TNF-α), a nonapoptotic necrotic cell death pathway mediated by death-domain receptors (DRs) that offers neuroprotection in a murine model of ischemic brain injury. Exhibits no effect on DR-induced apoptosis. Also acts as a selective and ATP-competitive inhibitor of RIP1 kinase with negligible effect of RIP2 kinase activity. Nec-1 target appears to be a critical common necroptotic step upstream of execution events and downstream of DRs. Inactive control, Nec-1i, is also available (Cat. No. 480066).	5 mg
Necrostatin-1, Inactive Control	**480066**	**5-(Indol-3-ylmethyl)-2-thiohydantoin, Nec-1i** A cell-permeable N-demethylated thiohydantoin analog of Nec-1 (Cat. No.480065) that is devoid of anti-necroptotic properties and serves as a suitable inactive control.	5 mg

Other Selected Inhibitors of Apoptosis

Product	Cat. No.	Comments	Size
Apoptosis Inhibitor	**178488**	**[M50054; 2,2'-Methylenebis(1,3-cyclohexanedione)]** A cell-permeable inhibitor of apoptosis induction (IC_{50} = 67 µg/ml in FasL-stimulated WC8 cells, 130 µg/ml in etoposide-stimulated U937 cells). Effects attributable to the inhibition of caspase-3 activation but does not directly inhibit caspase-3 even at 1 mg/ml.	10 mg
Apoptosis Inhibitor II, NS3694	**178494**	**(NS3694)** A cell-permeable diarylurea compound that specifically prevents the active ~700-kDa apoptosome complex formation triggered by cytochrome *c* release, thus blocking apoptosome-mediated caspase activation and cell death (50 µM completely blocks TNF-α-induced death in MCF-casp3 cells). Unlike M50054 (Cat. No.178488), NS3694 exhibits no effect on apoptosome-independent caspase activation and cell death induced by FasL. Inhibits neither cytochrome *c* release nor the enzymatic activity of caspases.	10 mg
Bax Channel Blocker	**196805**	**[(±)-1-(3,6-Dibromocarbazol-9-yl)-3-piperazin-1-yl-propan-2-ol, bis TFA]** A cell-permeable dibromocarbazolo-piperazinyl derivative that displays anti-apoptotic properties. Effectively blocks Bid-induced cyctochrome *c* release from HeLa cell mitochondria (~80% inhibition at 5 µM) by inhibiting Bax channel-forming activity (IC_{50} = 520 nM in a liposome channel assay).	5 mg
Bax-Inhibiting Peptide, Negative Control	**196811**	**(BIP-NC; H-IPMIK-OH)** A cell-permeable negative control of the Bax-Inhibiting Peptide, V5 (Cat. No.196810). Does not suppress Bax-mediated apoptosis (~200 µM).	5 mg
Bax-Inhibiting Peptide, V5	**196810**	**(BIP-V5; H-VPMLK-OH)** 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). Also effectively blocks caspase-independent necrotic cell death. Shown to be Ku70 competitive, interact with Bax, prevent its conformational change and mitochondrial translocation. Displays extended stability in culture medium (~3 days). Negative control peptide is also available (Cat. No.196811).	5 mg
Fas/FasL Antagonist, Kp7-6	**341291**	**(H-YC*DEHFC*Y-OH, Cyclic [Cys-Cys disulfide]; Kp7-6)** An exocyclic cystine-knot peptide that 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 andPF092) and Fas (CD95/APO-1) with comparable affinity (K_d = 11.2 & 13.2 µM, respectively), resulting in disabled receptor ensembles and altered signaling pathways. Shown to prevent Con A (Cat. No.234567)-induced liver injury in a murine hepatitis model *in vivo*. Does not bind to TNF-α or TNFR.	25 mg
Humanin, Human, Synthetic	**400140**	**(H-MAPRGFSCLLLLTSEIDLPVKRRA-OH; HN)** A 24-residue anti-apoptotic peptide that, when expressed intracellularly, offers protection against neuronal apoptosis induced by presenilin and APP (amyloid precursor protein) mutants associated with familial Alzheimer's disease (AD). Shown to reduce cytochrome *c* release *in vitro* by directly binding to Bax (Bcl-2-associated X protein; K_d ~ 2 nM) and preventing its association with isolated mitochondria.	1 mg

Other Selected Inhibitors of Apoptosis *continued*

Product	Cat. No.	Comments	Size
Omi/HtrA2 Protease Inhibitor, Ucf-101	**496150**	**{High Temperature Requirement A2 Inhibitor I; 5-[5-(2-Nitrophenyl) furfurylidine]-1,3-diphenyl-2-thiobarbituric Acid}** A cell-permeable furfurylidine-thiobarbituric acid compound that acts as a potent, specific, competitive, and reversible inhibitor of the pro-apoptotic, heat-inducible, mitochondrial serine protease Omi/HtrA2 (IC_{50} = 9.5 µM for His-$Omi_{134-458}$). Shows very little activity against various other serine proteases tested (IC_{50} ≥ 200 µM). Reported to block Omi/HtrA2 induced cell death in caspase-9 (-/-) null fibroblasts.	10 mg
Pifithrin-α	**506132**	**[2-(2-Imino-4,5,6,7-tetrahydrobenzothiazol-3-yl)-1-*p*-tolylethanone, HBr]** A cell-permeable chemical inhibitor of p53. Reversibly inhibits p53-dependent transactivation of p53-responsive genes and reversibly blocks p53-mediated apoptosis. Inhibits p53-dependent growth arrest of human diploid fibroblasts in response to DNA damage but has no effect on p53-deficient fibroblasts. Protects normal tissues from the deleterious side effects of chemotherapy. Has been reported to protect neurons against ß-amyloid peptide and glutamate-induced 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. A chemical inhibitor of p53. Reversibly inhibits p53-dependent transactivation of p53-responsive genes; also reversibly blocks p53-mediated apoptosis. Acts as a P-gp modulator by changing relative substrate specificity of the transporter. This compound has been reported to be a potent STAT6 transcriptional inhibitor.	10 mg

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Amyloidogenesis Inhibitors

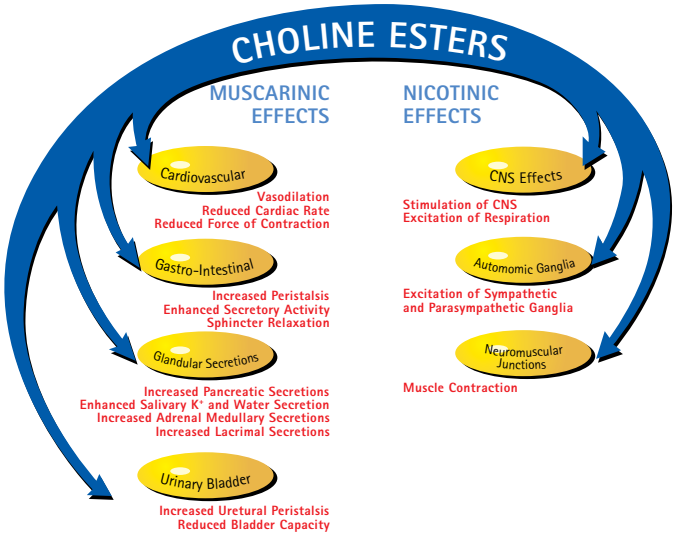
Aß (ß-amyloid peptide) is a major component of neuritic plaques and cerebrovascular amyloid deposits in the brains of patients with Alzheimer's disease (AD). The cellular origin of amyloid precursor protein (APP) that give rise to Aß is now well understood. Morphological evidence suggests that APP-immunoreactive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

Amyloidogenesis Inhibitors

Product	Cat. No.	Comments	Size
Amyloid Precursor Protein ß-Secretase Inhibitor	**171601**	**KTEETSEVN(stat)VAEF** A potent inhibitor of the amyloid precursor protein (APP) ß-secretase (IC_{50} = 30 nM).	500 µg
$Aß_{40}$ Fibrillogenesis Inhibitor	**171581**	**[Aß16-20m; Ac-K(Me)LV(Me)FF-NH_2; Amyloid $ß_{40}$ Fibrillogenesis Inhibitor]** A membrane-permeable pentapeptide based on the core domain of ß-Amyloid (Aß) that contains N-methyl amino acids in alternate positions. Acts as a selective inhibitor of $Aß_{40}$ fibrillogenesis and disassembles preformed fibrils (IC_{50} expressed as a molar ratio of inhibitor to $Aß_{40}$ = 6.9 and 7.8, respectively). Exists as a monomer in solution and appears to function as a ß-sheet breaker. Displays greater stability towards denaturation and is resistant to chymotrypsin.	1 mg 5 mg
$Aß_{42}$ Fibrillogenesis Inhibitor II	**171587**	**(Amyloid $ß_{42}$ Fibrillogenesis Inhibitor II; RVVIA-NH_2)** A pentapeptide amide that contains the C-terminal sequence of $Aß_{42}$ with Gly^{38} to Arg substitution. Acts as a ß-sheet breaker. Binds to the seeding sequence of $Aß_{42}$ peptide and interferes with its aggregation. At ~5-fold excess concentration, it offers protection against $Aß_{42}$ induced neurotoxicity in SH-SY5Y neuroblastoma cells. The replacement of Gly^{38} with Arg results in improved aqueous solubility and potency resulting from its ability to form salt bridges.	5 mg
$Aß_{42}$ Fibrillogenesis Inhibitor III	**171588**	**(Amyloid $ß_{42}$ Fibrillogenesis Inhibitor III; Ac-LPFFD-NH_2; iAß5p)** A modified analog of $Aß_{42}$ Fibrillogenesis Inhibitor I (Cat. No.171586) that crosses the blood-brain barrier and acts as a ß-sheet breaker. Reported to increase neuronal survival and reduce brain inflammation in a transgenic mouse model of Alzheimer's disease, probably due to a reduction in Aß deposits. Displays greater stability against proteolytic degradation ($t_{1/2}$ > 24 hours in human plasma and cerebrospinal fluid; ~ 37 minutes in blood).	5 mg
Clioquinol	**233165**	**(5-Chloro-7-iodo-8-hydroxyquinoline)** 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 the Cu^{2+} and Zn^{2+} that stud these deposits. Shown to increase distal dominant axonopathy in animal models.	1 g
Diclofenac Sodium	**287840**	A cell-permeable, non-selective cyclooxygenase inhibitor (IC_{50} = 60 nM and 200 nM for ovine COX-1 and COX-2 respectively) and potent non-steroidal anti-inflammatory drug with analgesic activity. Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. Also inhibits liver phenol sulfotransferase activity (IC_{50} = 9.5 µM).	1 g
Flurbiprofen	**344079**	A mixture of S(+) and R(–) enantiomers. A cell-permeable, non-steroidal anti-inflammatory agent that acts as a potent inhibitor of cyclooxygenase (IC_{50} = 5 nM for LPS-induced COX in human peripheral blood cells). Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. Suppresses iNOS expression in RAW 264.7 macrophages. Reduces microglial activation and ß-amyloid deposit in APP+PS1 transgenic mice.	100 mg
Genistein	**345834**	A cell-permeable, reversible, substrate competitive inhibitor of protein tyrosine kinases, including autophosphorylation of epidermal growth factor receptor kinase (IC_{50} = 2.6 µM). The inhibition is competitive with respect to ATP and non-competitive with respect to the phosphate acceptor. Has only a trivial effect on the activity of PKA and PKC (IC_{50} > 350 µM). Inhibits tumor cell proliferation and induces tumor cell differentiation. Produces cell cycle arrest and apoptosis in Jurkat T-leukemia cells. However, it prevents anti-CD3 monoclonal antibody-induced thymic apoptosis. Also inhibits topoisomerase II activity *in vitro*.	20 mg 50 mg
Resveratrol	**554325**	A phenolic product found in both grape skins and wines. Has antifungal, antitumor, and antioxidative properties. A specific inhibitor of cyclooxygenase-1 (COX-1; ED_{50} = 15 µM). Also inhibits the hydroxyperoxidase activity of COX-1 (ED_{50} = 3.7 µM). Strongly inhibits insoluble transthyretin (TTR) amyloid fibril formation. Inhibits phorbol ester-induced free radical formation in HL-60 cells (ED_{50} = 27 µM) and acts as an anti-mutagenic agent (ED_{50} = 15 µM) in TM677 cells treated with DMBA. Also a selective inhibitor of P450 1A1. Reported to activate sirtuins and promote the survival of eukaryotic cells.	25 mg

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 (AD). 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**	**(DFP)** Serine protease inhibitor. A potent, irreversible inactivator of acetylcholinesterase that can cross the blood-brain barrier. Selectively blocks T cell receptor-triggered programmed cell death in murine T cell hybridoma and in activated peripheral T cells.	1 g
Galanthamine, Hydrobromide	**345670**	**(Nivalin, HBr)** A competitive and reversible inhibitor of acetylcholinesterase. Antimyasthenic agent. Can partially reverse the effects of scopolamine-induced amnesia in rats. Reported to improve learning and short-term memory in animal models.	20 mg
(±)-Huperzine A	**385885**	Synthetic, optically inactive, enantiomeric mixture. Reportedly used as a memory enhancing agent; may also act as a cholinomimetic. Inhibits brain acetylcholinesterase activity.	1 mg

Monoamine Oxidase Inhibitors

Product	Cat. No.	Comments	Size
Quinacrine, Dihydrochloride	**551850**	A non-specific phospholipase A_2 (PLA_2) inhibitor. Acts as an acetylcholine receptor antagonist. Suppresses glibenclamide-sensitive K^+-currents (IC_{50} = 4.4 µM). Also inhibits monoamine oxidase (MAO).	100 mg

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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, the level of Aβ peptides is 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 Aβ 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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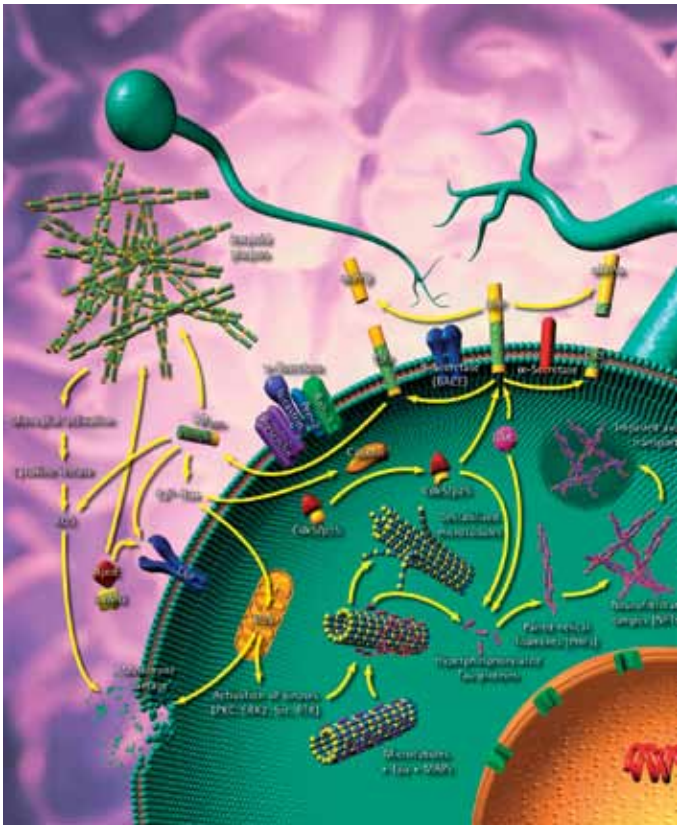

Secretase Inhibitors

Product	Cat. No.	Comments	Size
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). A valuable tool for distinguishing among different types of ATPases. Blocks lysosomal cholesterol trafficking in macrophages and is known to interfere with pH regulation in brain cells. Exhibits cytotoxic effects on a number of cell lines in a cell viability assay. Reported to selectively inhibit ß-secretase, an enzyme involved in the processing of amyloid precursor protein (APP).	10 µg
MG-132 (Z-LLL-CHO)	**474790**	**(Carbobenzoxy-L-leucyl-L-leucyl-L-leucinal; Z-LLL-CHO)** 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. Activates c-Jun N-terminal kinase (JNK1), which initiates apoptosis. Inhibits NF-κB activation (IC_{50} = 3 µM). Prevents ß-secretase cleavage. A 10 mM (1 mg/210 µl) solution of MG-132 (Cat. No.474791) in DMSO is also available.	1 mg 5 mg
InSolution™OM99-2	**496000**	**(EVNLΨAAEF)** An eight residue peptidomimetic, tight binding transition-state analog inhibitor of human brain memapsin 2 (K_i = 1.6 nM, recombinant memapsin 2; K_i = 9.58 nM, recombinant pro-memapsin 2). Also inhibits cathepsin D (K_i = 48 nM). This aspartyl protease inhibitor is designed from the template of the ß-secretase site of Swedish ß-amyloid precursor protein (APP) with Asp to Ala replacement; also includes a nonhydrolyzable hydroxyethylene isostere between Leu and Ala.	250 µg
Pepstatin A Methyl Ester	**516485**	**(Isovaleryl-V V-Sta-A-Sta-OCH_3; PME)** 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 in solubilized 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). Sta = (3S,4S)-4-Amino-3-hydroxy-6-methyl-heptanoic acid.	1 mg
SB 225002	**559405**	**N-(2-Hydroxy-4-nitrophenyl)-N'-(2-bromophenyl)urea** A potent, selective, and competitive antagonist of the G-protein coupled receptor CXCR2 (IL-8RB; IC_{50} = 22 nM for the inhibition of ^{125}I-IL-8 binding to CXCR2). Shows ~150-fold selectivity over CXCR1. Inhibits human and rabbit neutrophil chemotaxis induced by both IL-8 and GROα *in vitro* and *in vivo* selectively blocks IL-8-induced neutrophil margination in rabbits. Reduces presenilin expression, inhibits γ-secretase activity, and blocks Aß40/42 production and notch processing; further, demonstrates *in vivo* efficacy in mouse models.	1 mg
γ-Secretase Inhibitor I	**565750**	**(Z-LLNle-CHO)** Cell permeable. Inhibits γ-secretase, a protease that cleaves the Amyloid Precursor Protein (APP) to generate ß-amyloid protein. Inhibition of this enzyme is believed to aid in the prevention of Alzheimer's disease.	1 mg
g40-Secretase Inhibitor I	**565765**	**[N-*trans*-3,5-Dimethoxycinnamoyl)-Ile-leucinal; t-3,5-DMC-IL-CHO]** A potent, cell-permeable, reversible γ-secretase inhibitor that preferentially appears to inhibit the secretion of $Aß_{1-40}$ (>90%) over $Aß_{1-42}$ (~15%). $Aß_{total}$ IC_{50} ~ 15 µM; $Aß_{1-40}$ IC_{50} ~ 22 µM; $Aß_{1-42}$ IC_{50} > 50 µM in CHO cells stable transfected with the cDNA encoding ßAPP695. Reported to be about 10-fold more potent than Z-Val-Phe-CHO (MDL 28170; Cat. No.208722).	1 mg
ß-Secretase Inhibitor II	**565749**	**(N-Benzyloxycarbonyl-Val-Leu-leucinal; Z-VLL-CHO)** A potent, cell-permeable, and reversible inhibitor of ß-secretase. Corresponds to the ß-secretase cleavage site (VNL-DA) of the Swedish mutant Amyloid Precursor Protein (APP). Inhibits the formation of both $Aß_{total}$ (IC_{50} = 700 nM) and $Aß_{1-42}$ (IC_{50} = 2.5 µM) in Chinese hamster ovary (CHO) cells stable transfected with wild-type APP751.	1 mg 5 mg
γ-Secretase Inhibitor II	**565755**	**(MW167)** A cell-permeable, reversible and selective peptidomimetic inhibitor of γ-secretase (IC_{50} = 13 µM for Aß). Displays only weak inhibitory activity against calpain II (IC_{50} = 100 µM in a purified enzyme assay).	1 mg
γ_{40}-Secretase Inhibitor II	**565766**	**N-*tert*-Butyloxycarbonyl-Gly-Val-Valinal** A cell-permeable substrate-based γ-secretase inhibitor that is reported to preferentially (> 90%) inhibit Aß cleavage at site 40 vs. 42 in a dose-dependent fashion, in transiently transfected 293T cells overexpressing APP695NL.	1 mg 5 mg
γ-Secretase Inhibitor III	**565760**	**N-Benzyloxycarbonyl-Leu-leucinal** A cell-permeable, reversible inhibitor of γ-secretase that reduces the formation of both $Aß_{total}$ (IC_{50} = ~ 35 µM) and $Aß_{1-42}$ using Chinese hamster ovary (CHO) cultures stably transfected with Amyloid Precursor Protein-751. Reported to be nontoxic and specific for γ-secretase. Also reported to inhibit calpain (IC_{50} = 3 µM).	1 mg

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Secretase Inhibitors *continued*

Product	Cat. No.	Comments	Size
ß-Secretase Inhibitor III	**565780**	**(H-EVNstatineVAEF-NH_2; Inhibitor GL189)** A substrate analog inhibitor of ß-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 IV	**565761**	**[N-(2-Naphthoyl)-Val-phenylalaninal; 2-Naphthoyl-VF-CHO]** A cell-permeable, reversible inhibitor of γ-secretase. Equipotently inhibits the release of $Aß_{x-40}$ (ED_{50} = 2.6 µM) and $Aß_{x-42}$ (ED_{50} = 2.7 µM) in HEK293 cells stably transfected with the Amyloid Precursor Protein Swedish mutants.	1 mg
ß-Secretase Inhibitor IV	**565788**	A cell-permeable isophthalamide compound containing hydroxyethylamine motif that binds to BACE-1 active site and potently blocks its proteolytic activity (IC_{50} = 15 nM for BACE-1, human and 29 nM for sAPP_NF in HEK293-APP^{NFEV} cells). Displays greater selectivity over other aspartyl proteases (IC_{50} = 0.23 µM, 7.6 µM and >50 µM for BACE-2, cathepsin D, and renin, respectively).	1 mg
γ-Secretase Inhibitor IX	**565770**	**{DAPT; N-[N-(3,5-Difluorophenacetyl-L-alanyl)]-S-phenylglycine *t*-Butyl Ester}** A cell-permeable dipeptide that suppresses Aß production by blocking γ-secretase ($Aß_{total}$ IC_{50} = 115 nM, $Aß_{42}$ IC_{50} = 200 nM). Prevents $Aß_{34}$ generation in murine N2a cells and hAPP/hBACE-1 transfected human HEK 293 cells. Reported to be functionally active in both HEK 293 cells and neuronal cultures without affecting the secretion of amyloid-ß precursor protein (APP). Also shown to lower Aß levels acutely in APP-transgenic mice. Reported to reduce extracellular Aß plaques and intracellular Aß accumulation in 3xTgAD transgenic mice. A 25 mM (5 mg/462 µl) solution of γ-Secretase Inhibitor IX (Cat. No.565784) in DMSO is also available.	5 mg
InSolution™ γ-Secretase Inhibitor IX	**565784**	**{DAPT; N-[N-(3,5-Difluorophenacetyl-L-alanyl)]-S-phenylglycine *t*-Butyl Ester}** A 25 mM (5 mg/462 µl) solution of γ-Secretase Inhibitor IX (Cat. No. 565770) in DMSO.	5 mg
γ-Secretase Inhibitor V	**565762**	**(N-Benzyloxycarbonyl-Leu-phenylalaninal; Z-LF-CHO)** A cell-permeable, reversible inhibitor of γ-secretase that is reported to inhibit the release of $Aß_{x-40}$ (ED_{50} = 5 µM) in HEK293 cells stably transfected with the Amyloid Precursor Protein Swedish mutants.	1 mg
γ-Secretase Inhibitor VI	**565763**	**{1-(S)-*endo*-N-(1,3,3)-Trimethylbicyclo[2.2.1]hept-2-yl)-4-fluorophenyl Sulfonamide}** Cell permeable. Potently inhibits $Aß_{42}$ production (IC_{50} = 1.8 µM). Treatment of HEK293 cells with this inhibitor results in ß-Secretase-cleaved APP fragments and secreted APPα, but no change in secreted APPsß is observed indicating specific inhibition of γ-secretase.	5 mg
γ-Secretase Inhibitor VII	**565768**	**[Compound A; MOC-LL-CHO (MOC = menthyloxycarbonyl)]** A cell-permeable reversible inhibitor of Aß and p3 secretion ($Aß_{40}$ IC_{50} = 2.3 µM; $Aß_{42}$ IC_{50} = 3 µM).	1 mg
InSolution™ γ-Secretase Inhibitor X	**565771**	**{L-685,458; {1S-Benzyl-4R-[1-(1S-carbamoyl-2-phenethylcarbamoyl)-1S-3-methylbutylcarbamoyl]-2R-hydroxy-5-phenylpentyl}carbamic Acid *tert*-butyl Ester}** A cell-permeable hydroxyethylene dipeptide isostere that acts as a highly specific and a potent inhibitor of γ-secretase ($Aß_{total}$ IC_{50} = 17 nM, $Aß_{40}$ IC_{50} = 48 nM, and $Aß_{42}$ IC_{50} = 67 nM in SHSY5Y cells overexpressing spßA4CTF). Binds to presenilin and blocks Notch intracellular domain production. Functions as a transition state analog mimic at the catalytic site of an aspartyl protease, however, it exhibits over 100-fold greater selectivity for γ-secretase than for cathepsin D.	250 µg
γ-Secretase Inhibitor XI	**565772**	**(7-Amino-4-chloro-3-methoxyisocoumarin; JLK6)** A cell-permeable, active site directed, irreversible serine protease inhibitor that belongs to the class of isocoumarin analogs. Acts as a potent and selective inhibitor of γ-secretase and blocks the production of both amyloid-$ß_{40}$ ($Aß_{40}$) and $Aß_{42}$ (IC_{50} < 100 µM) in HEK293 cells expressing wild-type and Swedish-mutant ß-amyloid precursor protein (APP).	5 mg
γ-Secretase Inhibitor XII	**565773**	**(Z-IL-CHO)** A cell-permeable, reversible dipeptide aldehyde that reduces Aß production by blocking γ-secretase activity *in vitro* ($Aß_{40}$ IC_{50} = 7.9 µM; $Aß_{42}$ IC_{50} = 7.6 µM) and in cultured CHO 2b-7 cells that stably overexpress APP695 ($Aß_{40}$ IC_{50} = 11.5 µM; $Aß_{42}$ IC_{50} = 8.3 µM). Also blocks the generation of CTFγ (γ-secretase-generated carboxyl-terminal fragment). Does not affect the formation of amyloid-ß-precursor protein (APP).	5 mg
γ-Secretase Inhibitor XIII	**565774**	**(Z-YIL-CHO)** A cell-permeable, reversible tripeptide aldehyde that reduces Aß production by blocking γ-secretase. Does not affect the formation of amyloid-ß precursor protein (APP). At 60 µM concentrations, abolishes nuclear localization of ErbB-4 receptor tyrosine kinase by inhibiting the formation of the s80 ErbB-4 fragment in T47-14 cells stimulated with TPA (Cat. No.524400).	5 mg

Secretase Inhibitors *continued*

Product	Cat. No.	Comments	Size
γ-Secretase Inhibitor XIV	**565775**	**[Z-Ct-Bu]-IL-CHO]** A cell-permeable, reversible tripeptide aldehyde that reduces Aß production by blocking γ-secretase *in vitro* ($Aß_{40}$ IC_{50} = 190 nM; $Aß_{42}$ IC_{50} = 780 nM) and in cultured CHO 2b-7 cells that stably overexpress APP695 ($Aß_{40}$ IC_{50} = 80 nM; $Aß_{42}$ IC_{50} = 120 nM). Does not affect the formation of amyloid-ß precursor protein (APP).	5 mg
InSolution™ γ-Secretase Inhibitor XIX	**565787**	**{(2S,3R)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-4-hydroxy-N-((3S)-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-butyramide}** A cell-permeable benzodiazepinyl-γ-hydroxybutyramide compound that acts as a highly potent γ-secretase inhibitor (IC_{50} = 60 pM towards $Aß_{40}$ secretion in SH-SY5Y cells overexpressing spßA4CTF).	100 µg
γ-Secretase Inhibitor XVI	**565777**	**(DAPM; N-[N-3,5-Difluorophenacetyl]-L-alanyl-S-phenylglycine Methyl Ester)** A cell-permeable γ-secretase inhibitor (IC_{50} Aß = ~10 nM in 7PA2 cells) with anti-aggregation properties. Prevents early Aß oligomerization by selectively blocking the Aß dimer and trimer formation.	5 mg
InSolution™ γ-Secretase Inhibitor XVII	**565778**	**(31C; WPE-III-31C)** A cell-permeable (hydroxyethyl)urea peptidomimetic that acts as a transition-state analog inhibitor of γ-secretase (IC_{50} = 300 nM for Aß production in intact cells). Binds the presenilin-γ-secretase complex (PS1-NTF, PS1-CTF, Nicastrin, and C83 APP CTF). Also inhibits the cleavage of N100Flag, a Notch-based substrate, and C100Flag, an APP-based substrate, in low nanomolar range.	500 µg
γ-Secretase Inhibitor XX	**565789**	A cell-permeable dibenzazepine (dbz) compound that acts as a potent γ-secretase inhibitor and significantly lowers both brain and plasma $Aß_{40}$ levels by ~72% in Tg2576 mutant APP transgenic mouse model (100 µmol/kg, b.i.d). Also potently inhibits Notch processing (IC_{50} = 1.7 nM in SupT1 cells) and induces conversion of proliferative crypt cells to post-mitotic goblet cells in both the C57BL/6 and Apc^{Min} mouse models (10 µmol/kg, i.p).	500 µg
γ-Secretase Inhibitor XXI	**565790**	A cell-permeable, potent, selective, peptidomimetic, non-transition-state analog inhibitor of γ-secretase and Notch processing (IC_{50} = 300 pM for $Aß_{40}$ in CHO cells overexpressing wild type ßAPP; 240 pM for $Aß_{40}$, 370 pM for $Aß_{42}$, and 320 pM for NICD, respectively, in HEK293 cells stably transfected with $ßAPP_{695}$ and mNotchΔE(M1727V); 100 pM for both $Aß_{40}$ and $Aß_{42}$ in SH-SY5Y cells stably transfected with SPA4CT). Lowers Aß levels in several APP transgenic mouse models. Reported to bind to presenilins and suppress the proteolytic cleavage of transmembrane protein substrates, including APLP1 and APLP2, CD44, ErbB4, E-cadherin, low density lipoprotein receptor-related proteins, Notch ligands, and $p75^{NTR}$. Only weakly affects presenilinase activity at much higher concentrations (200-400 µM).	500 µg
γ-Secretase Modulator, CW	**234515**	**[3,5-bis(4-Nitrophenoxy)benzoic acid]** A cell-permeable benzoate that effectively inhibits $Aß_{42}$ as well as $Nß_{25}$ (Notch-1 Aß-like 25-mer peptide; VKSEPVEPPLPSQLHLMYVAAAAFV) secretion during presenilin (PS)-dependent intramembrane proteolysis in cells.	100 mg

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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.

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Arginase Inhibitors

Product	Cat. No.	Comments	Size
BEC, Hydrochloride	**197900**	**[(S)-(2-Boronoethyl)-L-cysteine, HCl)]** A boronic acid-based arginine analog that acts as a slow-binding, competitive transition state inhibitor of arginases I and II (K_i = 310 nM for human recombinant type II arginase, pH 7.5). BEC does not inhibit nitric oxide synthase (NOS). Causes significant enhancement of NO-dependent smooth muscle relaxation in human penile corpus cavernosum tissue.	5 mg
DL-α-Difluoromethylornithine, Hydrochloride	**288500**	**(DFMO; Eflornithine; RMI-71782)** A cell-permeable, anticancer agent that acts as a specific and irreversible inhibitor of ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine biosynthesis. Inhibits B16 melanoma-induced angiogenesis *in ovo* and proliferation of vascular endothelial cells *in vitro*.	25 mg
N^G-Hydroxy-L-arginine, Monoacetate Salt	**399250**	**(NOHA, AcOH)** Cell permeable. A key intermediate in the biosynthesis of nitric oxide by constitutive nitric oxide synthase (cNOS). NOHA can be efficiently oxidized to nitric oxide and citrulline by cytochrome P450 system. A potent inhibitor of liver and macrophage arginase (K_i = 150 µM).	5 mg
N^ω-Hydroxy-nor-L-arginine, Diacetate Salt	**399275**	**[L-2-Amino-(4-(2'-hydroxyguanidino)butyric Acid, $2CH_3CO_2H$; nor-NOHA, $2CH_3CO_2H$]** A potent, selective, competitive, and high affinity inhibitor of arginase. Shown to inhibit arginase from rat liver (IC_{50} = 2 µM) and mouse macrophages (IC_{50} = 50 µM). Shown to specifically interact with the manganese-cluster of the enzyme active site. Does not function as a substrate or as an inhibitor for NOS. Hence, nor-NOHA may be a useful tool to study the interplays between arginase and NOS.	1 mg 5 mg

Glutathione S-Transferase (GST) Inhibitors

Glutathione S-transferases (GSTs) 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.

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Glutathione S-Transferase Inhibitors

Product	Cat. No.	Comments	Size
Caffeic Acid	**205546**	**(3,4-Dihydroxycinnamic Acid)** A natural dietary compound reported to have anti-carcinogenic and anti-inflammatory properties. A cell-permeable, selective, non-competitive inhibitor of 5-lipoxygenase (ID_{50} = 3.7 µM). Inhibits Cu^{2+}-induced LDL oxidation in the initiation phase but acts as a prooxidant in the propagation phase. An irreversible inhibitor of glutathione S-transferases and a non-competitive inhibitor of xanthine oxidase.	500 mg
Luteolin	**440025**	An antioxidant flavonoid and a free radical scavenger. Inhibits rat liver cytosolic glutathione S-transferase activity. Also shows cytotoxic effects on Raji lymphoma cells. Incubation of the non-tumor cell line C3H10T½CL8 with luteolin results in induction of p53 accumulation and apoptosis, with apoptosis occurring at the G_2/M phase of the cell cycle.	5 mg
Sulfasalazine	**573500**	A cell-permeable anti-inflammatory agent that acts as an inhibitor of glutathione-S-transferase (IC_{50} = 10 µM in HG9 cell line). Strongly inhibits NF-κB activation and potently induces apoptosis in T-lymphocytes. Causes neutrophil apoptosis that can be abrogated by tyrosine kinase inhibitors, protein kinase A inhibitors, or antioxidants. Also inhibits basic fibroblast growth factor-induced endothelial cell chemotaxis.	100 mg

Guanylate Cyclase (GC) Inhibitors

Guanylyl cyclase (GC) catalyzes the formation of the second messenger cyclic GMP (cGMP) from GTP and exists in both the soluble and particulate fractions. The soluble enzyme can be regulated by free radicals and nitrovasodialators, whereas the particulate enzyme can be regulated by various peptides. 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*.

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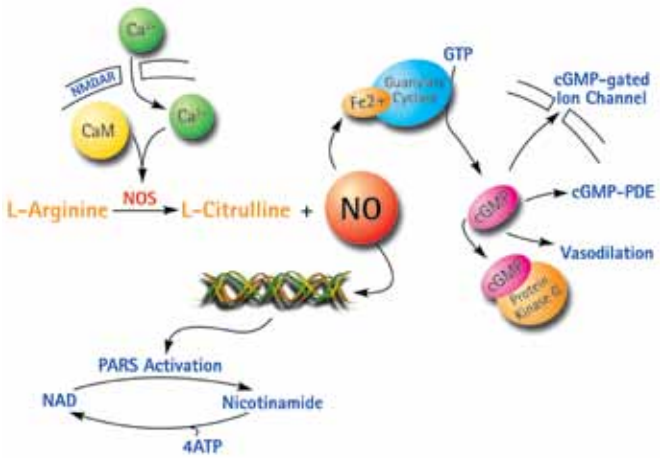

Guanylate Cyclase Inhibitors

Product	Cat. No.	Comments	Size
LY 83583	**440205**	**(6-Anilino-5,8-quinolinequinone)** A cell-permeable, 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. Shown to inhibit interleukin-1-induced cGMP accumulation in cultured rat aortic vascular smooth muscle cells. Also inhibits neutrophil chemotaxis induced by NO donors.	5 mg 25 mg
Methylene Blue	**457250**	**[3,7-*bis*(Dimethylamino)phenothiazin-5-ium Chloride]** Inhibitor of soluble guanylate cyclase. Organic spin-trap agent that forms stable adducts with oxygen free radicals in solution; biological staining agent. Dye content: ≥85%.	1 g
NS 2028	**492030**	**[4H-8-Bromo-1,2,4-oxadiazolo(3,4-d)benz(b)(1,4)oxazin-1-one]** 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**	**(1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one)** A cell-permeable, potent and selective inhibitor of nitric oxide (NO)-sensitive guanylyl cyclase (IC_{50} = 20 nM). In incubated cerebellum slices, ODQ reversibly inhibits the NO-dependent cGMP response to glutamate receptor agonists without affecting NOS activity. It does not chemically inactivate NO; however, it does inhibit cGMP generation in response to NO donors. ODQ does not inhibit NO-mediated macrophage toxicity, a phenomenon unrelated to cGMP, nor does it affect the activity of particulate guanylyl cyclase or adenylyl cyclase.	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 or NOS-3), and (c) an inducible enzyme (iNOS or NOS-2) that is associated with the cytotoxic function of macrophages. These enzymes exist as homodimers, each monomer consisting of two major domains: an N-terminal oxygenase domain and a C-terminal reductase domain. The interdomain linker contains the calmodulin-binding sequence. 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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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

Biological Activities of Selected Nitric Oxide Synthase Inhibitors (IC_{50} values in µM)

Product	Cat. No.	eNOS	iNOS	bNOS
1400W	100050	50*	0.007*	2*
Aminoguanidine, Hemisulfate	154500	526	250	
1-Amino-2-hydroxyguanidine, *p*-Toluensulfate	155200		68	
Dexamethasone	265005		0.005	
N^G,N^G-Dimethyl-L-arginine, Dihydrochloride	311203			
N^G,$N^{G'}$-Dimethyl-L-arginine, Dihydrochloride	311204			
Diphenyleneiodonium Chloride	300260	0.18	0.05	
2-Ethyl-2-thiopseudourea, Hydrobromide	341180	0.036†	0.017†	0.029†
Haloperidol	371980			31†
L-N^5-(1-Iminoethyl)ornithine, Dihydrochloride	400600	0.5	2.2	3.9
MEG, Hydrochloride	444600			
S-Methylisothiourea Sulfate (SMT)	466220		2.0‡	
S-Methyl-L-thiocitrulline, Dihydrochloride	472804	5.4	34	0.3

Product	Cat. No.	eNOS	iNOS	bNOS
N^G-Monomethyl-D-arginine, Monoacetate Salt	475892			
N^G-Monomethyl-L-arginine, Monoacetate (L-NMMA)	475886	0.7	3.9	0.65
N^G-Nitro-L-arginine Methyl Ester, Hydrochloride	483125	0.5		
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, Sodium Salt	484500			
7-Nitroindazole, 3-Bromo-, Sodium Salt	203912			
nNOS Inhibitor I	490070	314†	39†	0.12†
L-Thiocitrulline, Dihydrochloride	589411		3.6†	0.06†
N^G-Propyl-L-arginine	537200	8.5	180	0.057
SKF-525A, Hydrochloride	567300			90

Abbreviations: bNOS: brain nitric oxide synthase; eNOS: endothelial nitric oxide synthase; iNOS: inducible nitric oxide synthase.
Note: *: K_d; †:K_i; ‡: EC_{50}

Nitric Oxide Synthase (NOS) Inhibitors

Product	Cat. No.	Comments	Size
1400W	**100050**	**[N-(3-Aminomethyl)benzylacetamidine, 2HCl]** A selective, cell-permeable, irreversible, slow, tight-binding inhibitor of inducible nitric oxide synthase (iNOS; K_d = 7 nM). Suitable for use in both *in vitro* and *in vivo* systems. Has a protective effect against cerebral ischemia by reducing ischemic lesion volumes. Exhibits greater than 5000- and 200-fold potency against human iNOS relative to eNOS and nNOS, respectively, and greater than 1000-fold potency against rat iNOS relative to eNOS.	5 mg
Aminoguanidine, Hemisulfate	**154500**	An irreversible inhibitor of both constitutive (IC_{50} = 526 µM) and inducible (IC_{50} = 250 µM) NOS activity in homogenates of rat ileal and colonic tissue.	100 mg
Caveolin-1 Scaffolding Domain Peptide, Cell-permeable	**219482**	**AP-Cav** Caveolin-1 scaffolding domain peptide (C1-SD_{82-101}) fused at the N-terminus to the cell-permeable Antennapedia internalization sequence (43-58). This peptide is reported to block eNOS activity and cellular NO release *in vitro* and reduce inflammation and tumorigenesis *in vivo*. Caveolin-1 interacts with several lipid-modified signaling ligands, such as EGFR, eNOS, G-protein α-subunits, PKCα, H-Ras, and Src, via the C1-SD_{82-101} sequence.	1 mg
Caveolin-1 Scaffolding Domain Peptide, Cell-permeable, Negative Control	**219483**	**AP-Cav-X** A scrambled caveolin-1 scaffolding domain peptide (C1-SD_{82-101}) fused at the N-terminus to the Antennapedia internalization sequence (43-58). Serves as an useful negative control for studies using Caveolin-1 Scaffolding Domain Peptide, Cell-permeable (Cat. No.219482).	1 mg
Chlorpromazine, Hydrochloride	**215921**	**{2-Chloro-10-[3'-(dimethylamino)propyl]phenothiazine, HCl}** Inhibits calmodulin-dependent stimulation of cyclic nucleotide phosphodiesterase (IC_{50} = 17 µM). Acts as a peripheral vasodilator. Acts as an inhibitor of lysosomal sphingomyelinase and of TNF-α production. Inhibits nitric oxide synthase (NOS) in mouse brain and prevents lipopolysaccharide induction of NOS in murine lung. Shown to potently and specifically inhibit KSP/Eg5 (IC_{50} < 10 µM), and PLA2.	500 mg
Dexamethasone	**265005**	**(9α-Fluoro-16&talpha-methylprednisolone)** Most active and highly stable glucocorticoid. Causes a reduction in cyclin A and Cdk2 activity, and inhibition of G_1/S transition in osteoblasts. Inhibits the phosphorylation of retinoblastoma (Rb) protein. Inhibits the expression of inducible but not constitutive nitric oxide synthase in vascular endothelial cells (IC_{50} = 5 nM). Enhances active cation transport in aortic smooth muscle cells by stimulating the Na^+ - K^+ pump. Induces apoptosis in human thymocytes.	100 mg

Nitric Oxide Synthase (NOS) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Diphenyleneiodonium Chloride	**300260**	**(DPI)** A cell-permeable, irreversible inhibitor of endothelial nitric oxide synthase (eNOS). Shown to inhibit acetylcholine-induced relaxation of preconstricted rat thoracic aortic rings (IC_{50} = 180 nM). Also inhibits iNOS in macrophages (IC_{50} = 50 nM). Blocks K^+ and Ca^{2+} currents in arterial smooth muscle cells. Inhibitor of mitochondrial NADPH-ubiquinone oxido-reductase.	10 mg
2-Ethyl-thiopseudourea, Hydrobromide	**341180**	**(S-Ethyl-ITU, HBr; S-Ethylisothiourea, HBr)** A highly potent, cell-permeable and competitive inhibitor of the inducible (K_i = 17 nM), endothelial (K_i = 36 nM), and neuronal (K_i = 29 nM) human nitric oxide synthase isozymes.	100 mg
L-N^5-(1-Iminoethyl)ornithine, Dihydrochloride	**400600**	**(L-NIO, 2HCl)** A cell-permeable, more potent inhibitor of endothelial nitric oxide synthase (eNOS; IC_{50} = 500 nM) compared to other arginine analogs such as L-NAME (Cat. No.483125) and L-NMMA (Cat. No.475886). Inhibits acetylcholine-induced relaxation of rat aorta rings (IC_{50} = 2 µM) and causes a dose-dependent increase in mean arterial blood pressure in the rat (EC_{50} = 19.5 mg/kg).	20 mg
L-NIL, Dihydrochloride	**482100**	**[L-N^6-(1-Iminoethyl)lysine, DiHCl]** A cell-permeable, potent and selective inhibitor of nitric oxide synthase that exhibits about 28-fold greater selectivity for inducible nitric oxide synthase (IC_{50} = 3.3 µM) than for the rat brain constitutive enzyme (IC_{50} = 92 µM). Exhibits about 10-fold greater inhibitory potency than N^G-Monomethyl-L-arginine (L-NMMA; Cat. No.475886) in inhibiting γ-interferon-induced NO_2^- production (IC_{50} = 460 nM).	10 mg
L-Thiocitrulline, Dihydrochloride	**589411**	**2-Thioureido-L-norvaline** Cell-permeable selective inhibitor of constitutive nitric oxide synthase. Has significantly greater inhibitory activity on brain nitric oxide synthase (K_i = 60 nM) compared to inducible nitric oxide synthase(K_i = 3.6 µM).	10 mg
MEG, Hydrochloride	**444600**	**(Mercaptoethylguanidine, HCl)** A cell-permeable inhibitor of inducible nitric oxide synthase (iNOS) and a peroxynitrite scavenger. Exhibits potent anti-inflammatory activity. Causes a dose-dependent inhibition of COX-1 (IC_{50} = 20 µM) and COX-2 activity.	10 mg
Melatonin	**444300**	**(N-Acetyl-5-methoxytryptamine; 5-Methoxy-N-acetyltryptamine)** A hormone that has been postulated as the mediator of photo-induced anti-gonadotropic activity in photoperiodic mammals. Counteracts the apoptotic effects of etoposide in bone marrow cells. Melatonin receptors are coupled to a G-protein system. Exhibits antioxidant properties. Has neuroprotective effects against Aß peptides. Inhibits rat cerebellar nitric oxide synthase (NOS). Also acts as a peroxynitrite scavenger.	1 g
N^G,$N^{G'}$-Dimethyl-L-arginine, Dihydrochloride	**311204**	**(SDMA, 2HCl)** Cell permeable. Endogenous inhibitor of nitric oxide synthesis *in vitro* and *in vivo*. Does not exhibit any significant inhibitory effect on NOS activity.	25 mg
N^G,N^G-Dimethyl-L-arginine, Dihydrochloride	**311203**	**(ADMA, 2HCl)** A cell-permeable, reversible inhibitor of nitric oxide synthase *in vitro* (IC_{50} = 2-3 µM) and *in vivo*. Causes dose-dependent vasoconstriction and bradycardic effects.	25 mg
N^G-Nitro-L-arginine	**483120**	**(L-NNA; N^G-NO_2-L-Arg)** A cell-permeable, potent and reversible inhibitor of bNOS and eNOS (K_i = 25 nM for bNOS; K_i = 90 nM for eNOS). Inhibits iNOS at much higher concentrations (K_i = 8.1 µM). Causes a reduction in cardiac output and profound vasoconstriction.	100 mg
N^G-Nitro-L-arginine Methyl Ester, Hydrochloride	**483125**	**(L-NAME, HCl; N^ω-NO_2-L-Arg-OMe; N^G-NO_2-L-Arg-OMe)** Cell permeable. More soluble analog of arginine and a competitive, slowly reversible inhibitor of eNOS (IC_{50} = 500 nM). Causes a prolonged inhibition of acetylcholine-induced relaxation of rat aortic rings (IC_{50} = 400 nM).	100 mg
N^G-Propyl-L-arginine	**537200**	**(N-PLA; N^ω-Propyl-L-arginine)** A cell-permeable, potent, competitive, and time-dependent inhibitor of neuronal nitric oxide synthase (nNOS) (K_i = 57 nM for nNOS; K_i = 180 µM for iNOS; K_i = 8.5 µM for eNOS).	5 mg
NG-Monomethyl-D-arginine, Monoacetate Salt	**475892**	**(N^G-Me-D-Arg, AcOH; N^ω-Me-D-Arg; D-NMMA)** Cell permeable. Negative control for N^G-Monomethyl-L-arginine (L-NMMA; 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
NG-Monomethyl-L-arginine, Monoacetate Salt	**475886**	**(N^ω-Me-L-Arg; N^G-Me-L-Arg, AcOH; L-NMMA)** Cell permeable. L-Arginine analog that acts as a competitive inhibitor of all three isoforms of nitric oxide synthase (K_i = 700 nM for eNOS; K_i = 3.9 µM for iNOS; K_i = 650 nM for nNOS). Inhibits histamine- and acetylcholine-induced relaxation (K_i = 9.5 µM) of intact norepinephrine-constricted guinea pig pulmonary artery.	25 mg 50 mg 100 mg

Nitric Oxide Synthase (NOS) Inhibitors *continued*

Product	Cat. No.	Comments	Size
Nitric Oxide Synthase, Inducible, Inhibitor Set	**482760**	**iNOS Inhibitor 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). Supplied with an informational insert.	1 set
p-Nitroblue Tetrazolium Chloride	**484235**	**(NBT; Nitro BT)** NADPH-diaphorase substrate that competitively inhibits nitric oxide synthase (IC_{50} = 3-4 µM). A well-known scavenger of superoxide anions. Useful as a substrate for alkaline phosphatase, often in conjunction with BCIP (Cat. No.203788).	250 mg 1 g
7-Nitroindazole	**483400**	**(7-Ni)** A cell-permeable, reversible and competitive inhibitor of nitric oxide synthase (NOS) with high selectivity for the brain enzyme (IC_{50} = 710 nM) vs. iNOS (IC_{50} = 20 µM). Also inhibits bovine endothelial nitric oxide synthase (IC_{50} = 800 nM). Binds to the heme group of NOS.	100 mg
7-Nitroindazole, 3-Bromo-, Sodium Salt	**203912**	**(BrNINa)** Sodium salt of 3-Bromo-7-nitroindazole (Cat. No.203911) that is more soluble in aqueous solutions and still penetrates the brain.	10 mg
7-Nitroindazole, Sodium Salt	**484500**	**(7-NiNa)** 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
nNOS Inhibitor I	**490070**	**{(4S)-N-(4-Amino-5[aminoethyl]aminopentyl)-N'-nitroguanidine, TFA}** A cell-permeable, potent and highly selective inhibitor of neuronal nitric oxide synthase (nNOS); (K_i = 120 nM). Displays >2500-fold and 320-fold selectivity over eNOS and iNOS, respectively.	1 mg 5 mg
PPM-18	**529570**	**(2-Benzoylamino-1,4-naphthoquinone)** 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*. Does not directly affect the enzymatic activities of iNOS or eNOS.	10 mg
1-Pyrrolidinecarbodithioic Acid, Ammonium Salt	**548000**	**(Ammonium Pyrrolidinedithiocarbamate; APDC; PDTC, NH_4)** Cell permeable. Inhibits the induction of nitric oxide synthase activity in rat alveolar macrophages. Prevents apoptosis in human HL-60 cells and thymocytes, but induces apoptosis in human and rat smooth muscle cells. Inhibits NF-κB activation and HIV replication in lymphocytes.	100 mg
S-Methyl-L-thiocitrulline, Dihydrochloride	**472804**	**[N^{δ}-(S-Methyl)isothioureido-L-ornithine]** A cell-permeable inhibitor of nitric oxide synthase that exhibits about 17-fold greater selectivity for rat neuronal nitric oxide synthase (IC_{50} = 300 nM) compared to the endothelial enzyme (IC_{50} = 5.4 µM).	10 mg
S-Methylisothiourea, Sulfate	**466220**	**(2-Methyl-2-thiopseudourea, Sulfate; SMT)** A highly selective, cell-permeable inhibitor of inducible nitric oxide synthase (iNOS). Reported to be 10 to 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
SKF-525A, Hydrochloride	**567300**	**(Proadifen)** Cell permeable. Blocks glibenclamide-sensitive K^+ channels. Inhibits neuronal nitric oxide synthase (IC_{50} = 90 µM). Also inhibits hepatic drug metabolism by inhibiting the cytochrome P450 system. Stimulates endothelial cell prostacyclin production while inhibiting platelet thromboxane synthesis. Potentiates the action of many drugs *in vivo*.	1 g
Spermidine, Trihydrochloride	**56766**	Polyamine that plays an important role in the regulation of cellular proliferation and differentiation. Inhibits neuronal nitric oxide synthase.	5 g

Anthrax Lethal Factor (LF) Metalloprotease Inhibitors

Product	Cat. No.	Comments	Size
Anthrax Lethal Factor Protease Inhibitor III	176910	**[BI-11B3; 5-(5-(2-Chloro-5-trifluoromethyl-phenyl)-furan-2-ylmethylene)-4-oxo-2-thioxo-thiazolidin-3-yl)-acetic acid]** A cell-permeable, rhodanine-acetic acid analog that chelates the active site Zn^{2+} and acts as a potent inhibitor of anthrax lethal factor (LF) metalloproteinase (K_i = 32 nM). Has only a minimal inhibitory effect on MMP-2 and MMP-9. Shown to effectively prevent MAPKK1 proteolysis (50 < 5 µM). BI-11B3 has been shown to double the survival rates of mice challenged with anthrax spores and treated with ciprofloxin.	5 mg
Anthrax Lethal Factor Protease Inhibitor, In-2-LF	176901	**[Anthrax LF Protease Inhibitor; *Bacillus anthracis* LF Protease Inhibitor; In-2-LF]** A cell-permeable N-acetylated, C-hydroxamate derivative of a 14-mer peptide designed from the MEK-2 template that acts as a competitive inhibitor of Anthrax lethal factor (LF) metalloprotease (K_i = 1 nM). Also inhibits MEK-3 cleavage. Protects against Anthrax toxin induced cytotoxicity in RAW264.7 and J772.A1 cells.	1 mg

Calpain Inhibitors

Calpains belong to a family of calcium-dependent thiol-proteases that proteolyze a wide variety of cytoskeletal, membrane-associated, and regulatory proteins. Fifteen gene products of the calpain family are reported in mammals, which are classified as nine typical and six atypical calpains. Typical calpains are characterized by a C-terminal $Ca2^{+-}$ binding domain that includes EF-hand motifs, while atypical calpains lack this region, but often contain additional domains. Calpains do not generally function as destructive proteases, but act as calcium-dependent modulators that remove limited portions of protein substrates. Calpains respond to Ca^{2+} signals by cleaving specific proteins, frequently components of signaling cascades, thereby irreversibly modifying their function. Two major isoforms of calpain are reported in mammals, calpain-1 (µ-form) and calpain-2 (m-form). They are constitutively expressed in all tissues and differ in their calcium requirement for activation (~50 µM for calpain-1 and ~500 µM for calpain-2) and contain several calcium-binding sites, which allosterically affect the enzyme activity.

Calpain-1 and -2 exhibit about 55 to 65% sequence homology and are composed of an 80 kDa and a 30 kDa subunit. The 80 kDa subunit has the catalytic site and is unique to each isozyme, whereas the 30 kDa unit is the regulatory subunit and is common to both calpains 1 and 2. Several putative substrates of calpain-1 and -2 are known that are cleaved by both isoforms, but with different efficiencies. Recently, determinants for calpain-1 and -2 have been analyzed and it is shown that amino acid preferences extend over 11 residues around the scissile bond. Calpains prefer Leu, Thr, Val in the P2 position, Lys, Tyr, Arg in the P1 position, and proline in the region flanking the P2 - P'1 segment.

Calpain-3, another typical calpain was first described as a skeletal muscle-specific calpain isoform. However, subsequent studies have shown its presence in several other tissues. It is a 94 kDa enzyme that is structurally similar to calpain-1 and -2, however, it has an additional N-terminal sequence of 20 -30 amino acids.

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-activation of NMDA, kainate and AMPA receptors in the brain leads to sustained influx of Ca^{2+} through the voltage-gated calcium channels. Disturbances in calcium homeostasis result in the activation of several calcium-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. In Alzheimer's disease the ratio of active (76 kDa) to inactive (80 kDa) calpain-1 is reported to be much higher. Calpain 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. However, most of the inhibitors reported are active site targeted peptides and their limited cell permeability poses problems.

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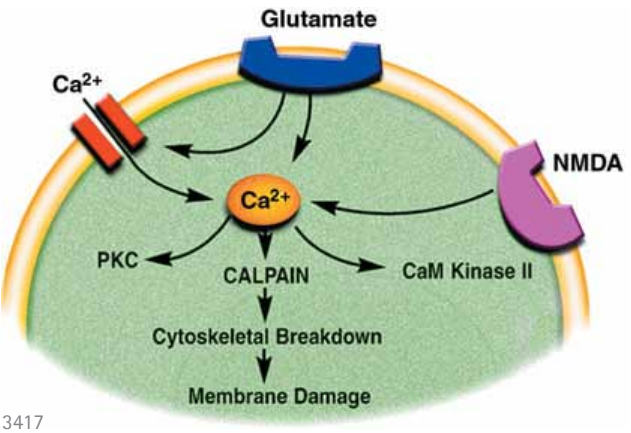

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Calpain Inhibitors

Product	Cat. No.	Comments	Size
ALLM	**208721**	**(Calpain Inhibitor II)** 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). Inhibits activation-induced programmed cell death and restores defective immune responses in HIV^+ donors. Blocks nitric oxide production by activated macrophages by interfering with transcription of the inducible nitric oxide synthase gene. A weak inhibitor of proteasome.	25 mg
ALLN	**208719**	**(Calpain Inhibitor I; LLNL; MG 101)** Cell-permeable 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). Inhibits neutral cysteine proteases and the proteasome (K_i = 6 µM). Modulates the processing of the ß-amyloid precursor protein (ßAPP) to ß-amyloid (Aß). Protects against neuronal damage caused by hypoxia and ischemia. Inhibits apoptosis in thymocytes and metamyelocytes. Also inhibits reovirus-induced apoptosis in L929 cells. Inhibits the proteolysis of IκB-α and IκB-ß by the ubiquitin-proteasome complex. Inhibits cell cycle progression at G_1/S and metaphase/anaphase in CHO cells by inhibiting cyclin B degradation. Also prevents nitric oxide production by activated macrophages by interfering with transcription of the inducible nitric oxide synthase gene. A 10 mM (5 mg/1.30 ml) solution of ALLN (Cat. No.208750) in DMSO is also available.	5 mg 25 mg
InSolution™ALLN	**208750**	**(Calpain Inhibitor I; LLNL; MG 101)** A 10 mM (5 mg /1.3 ml) solution of ALLN (Cat. No. 208719) in DMSO.	5 mg
Calpain Inhibitor III	**208722**	**(Carbobenzoxy-valinyl-phenylalaninal; MDL 28170)** A potent, cell-permeable inhibitor of calpain I and II (K_i = 8 nM). Reduces capsaicin-mediated cell death in cultured dorsal root ganglion. Reported to block A23187-induced suppression of neurite outgrowth in isolated hippocampal pyramidal neurons. Exhibits neuroprotective effect in glutamate-induced toxicity.	25 mg
Calpain Inhibitor IV	**208724**	**(Z-LLY-FMK)** A potent, cell-permeable, and irreversible inhibitor of calpain II (k_2 = 28,900 $M^{-1}s^{-1}$). Also acts as an inhibitor of cathepsin L (k_2 = 680,000 $M^{-1}s^{-1}$).	1 mg
Calpain Inhibitor Set	**208733**	Contains 5 mg of ALLN (Cat. No.208719), 25 mg of 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).	1 set
Calpain Inhibitor V	**208726**	**(Mu-Val-HPh-FMK)** A potent, cell-permeable, and irreversible inhibitor of calpain.	1 mg
Calpain Inhibitor VI	**208745**	**[*N*-(4-Fluorophenylsulfonyl)-L-valyl-L-leucinal; SJA6017]** A potent, cell-permeable, reversible inhibitor of calpain (IC_{50} = 7.5 nM for µ-calpain and 78 nM for m-calpain). Also potently inhibits cathepsin B (IC_{50} = 15 nM) and L (IC_{50} = 1.6 nM). Reduces bFGF-induced angiogenesis in rat cornea and prevents selenite cataract formation. Reduces A23187-induced nuclear opacity and proteolysis of crystallins and α-spectrin in cultured lenses.	1 mg 5 mg
Calpain Inhibitor XI	**208743**	**[Z-L-Abu-CONH$(CH_2)_3$-morpholine]** A cell-permeable dipeptidyl α-ketoamide that acts as a potent, highly selective, reversible, and active site inhibitor of calpain-1 and -2 (K_i = 140 nM and 41 nM, respectively). Weakly inhibits cathepsin B (K_i = 6.9 µM). Reported to have a neuroprotective role in the central nervous system following focal ischemia. Also protects against virus-induced apoptotic myocardial injury in mice.	1 mg 5 mg
Calpain Inhibitor XII	**208744**	**(Z-L-Nva-CONH-CH_2-2-Py)** A cell-permeable dipeptidyl α-ketoamide compound that acts as a potent, selective, reversible, and active site inhibitor of calpain-1 (K_i = 19 nM). Shown to inhibit calpain-2 (K_i = 120 nM) and cathepsin-B(K_i = 750 nM) at higher concentrations.	1 mg
Calpastatin Peptide	**208902**	**(CS Peptide)** A 27-amino acid, cell-permeable peptide encoded by exon 1B of human calpastatin that acts as a potent inhibitor of calpain I and calpain II (IC_{50} = 20 nM for purified rabbit calpain II). Does not inhibit either papain or trypsin. Blocks the down-regulation of protein kinase C (PKC) in rat pituitary GH_4C_1 cells stimulated by thyrotropin-releasing hormone (TRH).	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	**3340051**	**(Benzyloxycarbonylleucyl-norleucinal)** A cell-permeable calpain inhibitor (ID_{50} = 52 nM for calpain-1; ID_{50} = 34 nM for calpain-2; ID_{50} = 138 nM for papain). Inhibits the Ca^{2+}-stimulated cleavage of p35 to p25 by calpain. Modulates the processing of ß-amyloid precursor protein to ß-amyloid (Aß). Promotes neurite elongation in differentiating PC12 cells. Prevents Ca^{2+}-ionophore-induced degradation of actin binding protein and P_{235} in platelets. Inhibits myosin light chain phosphorylation in platelets stimulated by collagen, ionomycin, or thrombin. Inhibits the growth of estrogen receptor positive breast cancer cells.	5 mg 25 mg 100 mg

Calpain Inhibitors *continued*

Product	Cat. No.	Comments	Size
EST	**330005**	**[E-64d; (2S,3S)-*trans*-Epoxysuccinyl-L-leucylamido-3-methylbutane Ethyl Ester; Loxistatin]** A cell-permeable, irreversible inhibitor of cysteine proteases. Similar to E-64 (Cat. No.324890) but devoid of charged groups. Reported to inhibit calpain-1 activation. The inhibitory activity of EST has been attributed to E-64c, the free acid formed by hydrolysis of the ester *in vivo*. Used in animal models of muscular dystrophy.	1 mg
PD 145305	**513021**	A useful negative control for the calpain inhibitors PD 150606 (Cat. No.513022) and PD 151746 (Cat. No.513024). Can be used both *in vivo* and *in situ*.	1 mg
PD 150606	**513022**	**[3-(4-Iodophenyl)-2-mercapto-(Z)-2-propenoic Acid]** A cell-permeable, non-competitive, selective non-peptide calpain inhibitor [K_i = 210 nM for calpain-1 (Cat. Nos. 208712 and 208713) and 370 nM for calpain-2 (Cat. Nos. 208715 and 208718)] directed towards the calcium binding sites of calpain. Exhibits high specificity for calpains relative to other proteases, such as cathepsin B and cathepsin L. Does not shield calpain against inactivation by the active-site inhibitor *trans*-(epoxysuccinyl)-L-leucyl-amido-3-methylbutane. Reportedly prevents dexamethasone-induced apoptosis in thymocytes.	5 mg
PD 151746	**513024**	**[3-(5-Fluoro-3-indolyl)-2-mercapto-(Z)-2-propenoic Acid]** A cell-permeable, non-peptidic, and highly selective calpain inhibitor directed towards the calcium binding sites of calpain. Displays over 20-fold greater selectivity for calpain-1 (Cat. Nos. 208712 and 208713) over calpain-2 (Cat. Nos. 208715 and 208718) (K_i values: 260 nM and 5.33 µM, respectively). Has been shown to prevent cycloheximide-induced apoptosis.	2 mg

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 non-healing 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 fibroblasts to move within the wound.

Collagenase Inhibitors

Product	Cat. No.	Comments	Size
Collagenase Inhibitor I	**234140**	**(Z-PDLDA-NHOH)** A potent and specific inhibitor of vertebrate collagenases with IC_{50} values in the micromolar range.	5 mg
TAPI-0	**579050**	**{N-(R)-[2-(Hydroxyaminocarbonyl)methyl]-4-methylpentanoyl-L-naphthylalanyl-L-alanine Amide; TNF-α Protease Inhibitor-0}** A hydroxamate-based inhibitor of collagenase, gelatinase, and TACE (TNF-α converting enzyme/ADAM17; IC_{50} = 100 nM). Blocks spontaneous and PMA-induced release of TNF-α in transfected COS 7 cells.	1 mg

Collagenase Inhibitors *continued*

Product	Cat. No.	Comments	Size
TAPI-1	**579051**	**{N-(R)-[2-(Hydroxyaminocarbonyl)methyl]-4-methylpentanoyl-L-naphthylalanyl-L-alanine, 2-aminoethyl Amide; TNF-α Protease Inhibitor-1}** A structural analog of TAPI-0 (Cat. No.579050) with similar *in vitro* efficacy for the inhibition of MMPs and TACE (TNF-α converting enzyme/ADAM17). TAPI-1 also blocks the shedding of several cell surface proteins such as IL-6 receptor, p60 TNF receptor, and p80 TNF receptor. Blocks constitutive (IC_{50} = 8.09 µM) and muscarinic receptor-stimulated (IC_{50} = 3.61 µM) sAAPα release in HEK 293 cells expressing M3 muscarinic receptors. A 10 mM (500 µg/100 µl) solution of TAPI-1 (Cat. No.579050) in DMSO is also available.	1 mg
InSolution™TAPI-1	**579053**	A 10 mM (500 µg/100 µl) solution of TAPI-1 (Cat. No. 579051) in DMSO.	500 µg

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**	**(α_1-AT; 3.5S α_1-Glycoprotein; α_1-Proteinase Inhibitor)** A single polypeptide chain of 394 amino acids and three carbohydrate side chains linked to asparagine residues present at about 290 mg/100 ml in acute phase plasma. Serine protease inhibitor that also acts as a major physiological regulator of elastase. Inhibitor of neutrophil elastase, cathepsin G, and proteinase 3.	1 mg 5 mg
Caffeic Acid	**205546**	**(3,4-Dihydroxycinnamic Acid)** A natural dietary compound reported to have anti-carcinogenic and anti-inflammatory properties. A cell-permeable, selective, non-competitive inhibitor of 5-lipoxygenase (ID_{50} = 3.7 µM). Inhibits Cu^{2+}-induced LDL oxidation in the initiation phase but acts as a prooxidant in the propagation phase. An irreversible inhibitor of glutathione S-transferases and a non-competitive inhibitor of xanthine oxidase.	500 mg
Elastase Inhibitor I	**324692**	**(Boc-AAA-NHO-Bz; PPE Inhibitor)** Serine protease inhibitor. Inhibits porcine pancreatic elastase (PPE; k_i = 128 M^{-1} sec^{-1}) and thermitase (k_i = 1.14 x 10^3 M^{-1} sec^{-1}).	1 mg
Elastase Inhibitor II	**324744**	**(HNE Inhibitor; MeOSuc-AAPA-CMK; MSACK)** A potent irreversible inhibitor of human neutrophil elastase (HNE). Inhibition results from cross-linking of the catalytic residues His^{57} and Ser^{195}.	5 mg
Elastase Inhibitor III	**324745**	A potent irreversible inhibitor of human leukocyte elastase (HLE) (K_i = 10 µM). Protects against lung injury induced by instillation of elastase.	5 mg
Elastase Inhibitor IV	**324759**	**[N-(2-(4-(2,2-Dimethylpropionyloxy)phenylsulfonylamino)benzoyl)aminoacetic acid; N-(*o*-(*p*-Pivaloyloxybenzene)sulfonylaminobenzoyl)glycine]** A cell-permeable sulfanilide compound that acts as a potent, substrate-competitive, and highly specific inhibitor of neutrophil elastase (IC_{50} = 19-49 nM in rat, rabbit, hamster, human, and mouse leukocyte elastase). Displays >100-fold greater selectivity over pancreas elastase (IC_{50} = 5.6 µM). Does not inhibit trypsin, thrombin, plasmin, kallikrein, chymotrypsin, and cathepsin G even at concentrations as high as 100 µM. Effectively suppresses human neutrophil elastase-induced lung hemorrhage and skin capillary permeability *in vivo*. Also reported to inhibit mast cell Stat6-protease.	1 mg

Furin Inhibitors

Product	Cat. No.	Comments	Size
Furin Inhibitor I	**344930**	**Decanoyl-RVKR-CMK** A peptidyl chloromethylketone that binds to the catalytic site of furin and blocks its activity. Hence, it can be used as a high specificity cleavage inhibitor of viral glycoproteins and blocker of viral replication. Reported to block the shedding of MT5-MMP by furin and prevent the activation of MT5-MMP. Also shown to reduce the pro-peptide cleavage of BACE (β-site APP-cleaving enzyme).	1 mg
Furin Inhibitor II	**344931**	**Hexa-D-arginine** A polyarginine compound that acts as a potent, specific, and competitive inhibitor of furin (K_i = 106 nM). Inhibits Subtilisin-like proprotein convertase 4 (PACE4) and prohormone convertase 1 (PC1) at much higher concentration (K_i = 580 nM and 13 µM, respectively). Has a stimulatory effect on the activity of prohormone convertase 2 (PC2). The D-peptides are suggested to be more resistant to *in vivo* hydrolysis than L-peptides.	1 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 on the next page).* 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 = 10–50 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.

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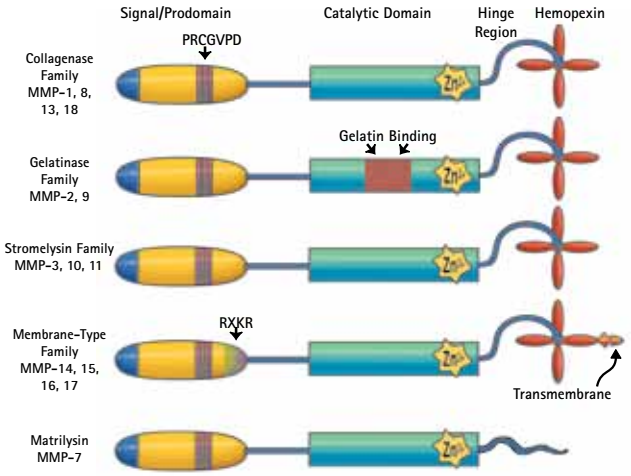

Matrix Metalloproteinase Inhibitors

Product	Cat. No.	Comments	Size
ADAMTS-5 Inhibitor	**114810**	**[Aggrecanase-2 Inhibitor; 5-((4-Chlorobenzylthio-3-trifluoromethyl-N-methyl-1H-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one]** A thioxothiazolidinone compound that possesses a Zn^{2+}-chelating structural motif and acts as an ADAMTS-5 (aggrecanase-2) inhibitor (IC_{50} = 1.1 µM) with ~40-fold selectivity over ADAMTS-4 (aggrecanase-1).	5 mg
Chlorhexidine, Dihydrochloride	**220557**	**1,6-bis[N'-(p-Chlorophenyl)-N5-biguanido]hexane, 2HCl, CH** An anti-microbial agent that acts as an inhibitor of MMP-2 and MMP-9; however, MMP-2 is more sensitive to chlorhexidine than MMP-9. Inhibits the collagenase activity of MMP-8 released by PMA-triggered polymorphonuclear leukocytes (PMNs) in a dose-dependent manner. CHX may possibly act through a cation-chelating mechanism.	100 mg
CL-82198	**233105**	A selective inhibitor of MMP-13 (IC_{50} = 10 µM). Binds to the S1' pocket of MMP-13 with its morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	5 mg
DL-Thiorphan	**598510**	**{N-[(RS)-2-Benzyl-3-mercaptopropanoyl]-glycine}** A thiol containing amido-acid that selectively binds to the active site zinc of metalloproteinases and blocks their activity (IC_{50} = 2.1 nM for neutral endopeptidase-NEP). Although it is shown to inhibit the activity for Aß peptide degrading enzyme neprilysin *in vitro*, it has no effect on the secretion of Aß peptide or amyloid ß precursor protein (APP). Also reported to inhibit the activity of angiotensin-converting enzyme (ACE) at much higher concentrations (IC_{50} = 14 µM); however, it does not affect the activity of endothelin-converting enzyme.	10 mg
Doxycycline, Hyclate	**324385**	**α-6-Deoxy-5-hydroxytetracycline** A commonly-used broad-spectrum antibiotic. A potent inhibitor of MMP-8 (neutrophil collagenase; IC_{50} = 30 µM) relative to MMP-1 (interstitial collagenase; IC_{50} = 300 µM). Also inhibits collagen synthesis by bovine articular chondrocytes cultured in alginate (IC_{50} = 25 µM). Inhibits nitric oxide synthesis by LPS-activated macrophages without affecting IL-10 release.	1 g
GM 1489	**364200**	**{N-[(2R)-2-(Carboxymethyl)-4-methylpentanoyl]-L-tryptophan-(S)-methyl-benzylamide}** A potent broad-range inhibitor of matrix metalloproteinases (MMPs). Inhibits MMPs *in vitro* (K_i = 0.2 nM for MMP-1; K_i = 500 nM for MMP-2; K_i = 20 µM for MMP-3; K_i = 100 nM for MMP-8; and K_i = 100 nM for MMP-9). Also reduces the inflammatory and the hyperproliferative responses that occur following topical phorbol ester application.	1 mg 5 mg
GM 6001	**364205**	**{Galardin; N-[(2R)-2-(Hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan Methylamide}** A potent, cell-permeable, broad-spectrum hydroxamic acid inhibitor of matrix metalloproteinases (MMPs); (K_i = 400 pM for MMP-1; K_i = 500 pM for MMP-2; K_i = 27 nM for MMP-3; K_i = 100 pM for MMP-8; and K_i = 200 pM for MMP-9). Prevents the release of TNF-α *in vivo* and *in vitro* and abrogates endotoxin-induced lethality in mice. A 10 mM (1 mg/257 µl) solution of GM6001 (Cat. No.364206) in DMSO is also available.	1 mg 5 mg
GM 6001, Negative Control	**364210**	**(N-*t*-Butoxycarbonyl-L-leucyl-L-tryptophan Methylamide)** A useful negative control for the MMP inhibitor GM 6001 (Cat. No.364205).	1 mg 5 mg
InSolution™GM6001	**364206**	A 10 mM (1 mg/257 µl) solution of GM6001 (Cat. No. 364205) in DMSO.	1 mg

Matrix Metalloproteinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Minocycline, Hydrochloride	**475843**	**7-Dimethylamino-6-demethyl-6-deoxytetracycline, HCl** Semi-synthetic tetracycline derivative effective against tetracycline-resistant staphylococci. A matrix metalloproteinase (MMP) inhibitor shown to inhibit tumor-induced angiogenesis. Inhibits stromelysin (MMP-3; IC_{50} = 290 µM) but does not inhibit other MMPs such as fibroblast collagenase or gelatinase. Potently inhibits PARP-1 (K_i = 13.4 nM) in a NAD^+ - competitive manner. Exhibits anti-inflammatory effects and suppresses T cell proliferation.	50 mg
MMP Inhibitor I	**444250**	**(FN-439)** A tetrapeptidyl hydroxamic acid that inhibits MMP-1 and MMP-8 (IC_{50} = 1.0 µM), MMP-9 (IC_{50} = 30 µM) and MMP-3 (IC_{50} = 150 µM). Retains its activity even after prolonged incubation with PRONASE® Protease (Cat. Nos. 53702 or 537088) or human granulocyte elastase.	10 mg
MMP Inhibitor II	**444247**	**{N-Hydroxy-1,3-di-(4-methoxybenzenesulphonyl)-5,5-dimethyl-[1,3]-piperazine-2-carboxamide}** A potent, reversible, broad-range inhibitor of matrix metalloproteinases. Inhibits 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 cell-permeable, reversible inhibitor of matrix metalloproteinases (supplied as a racemic mixture). 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**	**(HONH-COCH$_2$CH$_2$CO-FA-NH$_2$)** A peptide hydroxamic acid that is shown to potently inhibits MMPs and pseudolysin from *P. aeruginosa*.	5 mg
MMP Inhibitor Set I	**444255**	Contains 5 mg each of MMP-2/MMP-9 Inhibitor I (Cat. No.444241) and MMP-3 Inhibitor II (Cat. No.444225), and 1 mg each of GM 6001 (Cat. No.364205), GM 6001, Negative Control (Cat. No.364210), and MMP-8 Inhibitor I (Cat. No.444237).	1 set
MMP Inhibitor V	**444290**	**[ONO-4817; (2S,4S)-N-Hydroxy-5-ethoxymethyloxy-2-methyl-4-(4-phenoxybenzoyl)aminopentanamide]** An orally active non-peptidyl hydroxamate compound that acts as an effective broad-spectrum inhibitor against MMP-2, -3, -8, -9, -12, -13 (K_i = 0.73, 42, 1.1, 2.1, 0.45, and 1.1 nM, respectively), but not MMP-1 (IC_{50} = 1.6 µM), MMP-7 (K_i = 2.5 µM), or other serine proteases (no activity against chymotrypsin or plasmin at 100 µM). Widely used in studying MMP-mediated diseases development *in vivo*. Also reported to block P-LAP secretase activity (≥70% inhibition of P-LAP shedding at 10 µM) that is otherwise not inhibited by TIMP-1/2 in CHO cell cultures *in vitro*.	2 mg
MMP-13 Inhibitor	**444283**	**[Pyrimidine-4,6-dicarboxylic acid, bis-(4-fluoro-3-methyl-benzylamide)]** A pyrimidine dicarboxamide compound that potently inhibits MMP-13 activity (IC_{50} = 8 nM) with expected selectivity over MMP-1, -2, -3, -7, -8, -9, -10, -12, -14 and -16 as determined by conformational structure analysis. Shown to bind to the MMP-13 catalytic domain and act as a non-zinc-chelating inhibitor.	1 mg
MMP-2 Inhibitor I	**444244**	**(OA-Hy; *cis*-9-Octadecenoyl-N-hydroxylamide; Oleoyl-N-hydroxylamide)** A cell-permeable, potent inhibitor of MMP-2 that acts in a dose-dependent manner (K_i = 1.7 µM).	10 mg
MMP-2 Inhibitor II	**444286**	An oxirane analog of SB-3CT, *p*MS (Cat. No. 444285) that acts as a selective, active site-binding, irreversible inhibitor of MMP-2 (K_i = 2.4 µM). Although less potent, it exhibits enhanced selectivity towards MMP-2 (K_i = 45 and 379 µM for MMP-1 and MMP-7, respectively) than SB-3CT, *p*MS.	5 mg
MMP-2 Inhibitor III	**444288**	**[(2-((Isopropoxy)-(1,1'-biphenyl-4-ylsulfonyl)-amino))-N-hydroxyacetamide]** A cell-permeable biphenylsulfonamido-hydroxamate compound that acts a potent and Zn^{2+}-binding site-targeting inhibitor of MMP-2 (IC_{50} = 12 nM). It exhibits good selectivity over MMP-9 and MMP-3 (IC_{50} = 0.2 and 4.5 µM, respectively) and shows practically no effect towards MMP-1 and MMP-7 (IC_{50} > 50 µM). Shown to effectively suppress the invasiveness of HT1080 sarcoma cells grown on matrigel.	5 mg
MMP-2/MMP-3 Inhibitor I	**444239**	**{N-[[(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)amino] carbonyl]-L-phenylalanine Methyl Ester}** 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**	**{α-[[[4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)amino]carbonyl] amino]-((2-pyridyl)piperazinyl)-(S)-benzenepropanamide}** A potent inhibitor of MMP-2 (K_i = 1.5 µM) and MMP-3 (K_i = 520 nM).	2 mg

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Matrix Metalloproteinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
MMP-2/MMP-3 Inhibitor III, PD166793	**444284**	**[(S)-2-(4'-Bromo-biphenyl-4-sulfonylamino-3-methylbutyric acid)]** A cell-permeable biphenylsulfonylvaline compound that acts as a potent inhibitor against MMP-2, -3, and -13 (IC_{50} = 47, 12, and 8 nM, respectively) and a weaker inhibitor against AMP deaminase (20% inhibition at 0.1 µM), MMP-1, -7, -9, and -14 (IC_{50} = 6.1, 7.2, 7.9, and 0.24 µM, respectively). Shown to offer therapeutic benefits *in vivo* in various animal models of heart failure and diabetes.	5 mg
MMP-2/MMP-9 Inhibitor I	**444241**	**{(2R)-2-[(4-Biphenylylsulfonyl)amino]-3-phenylpropionic Acid}** A potent inhibitor of MMP-2 (IC_{50} = 310 nM) and MMP-9 (IC_{50} = 240 nM). Orally active in animal models of tumor growth and metastasis.	5 mg
MMP-2/MMP-9 Inhibitor II	**444249**	**{(2R)-[(4-Biphenylylsulfonyl)amino]-N-hydroxy-3-phenylpropionamide}** A potent inhibitor of MMP-2 (IC_{50} = 17 nM) and MMP-9 (IC_{50} = 30 nM). Also shown to potently induce and rapidly activate HIF. Reported to inhibit Lewis lung carcinoma-induced lung colonization in a murine model.	1 mg
MMP-2/MMP-9 Inhibitor III	**444251**	A hydrophobic cyclic peptide that acts as a potent inhibitor of MMP-2 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. Also, phage that display this peptide specifically targets angiogenic blood vessels *in vivo*.	1 mg
MMP-2/MMP-9 Inhibitor IV	**444274**	**(SB-3CT)** A potent, selective, slow-binding and mechanism-based inhibitor of human gelatinases, MMP-2 (K_i = 13.9 nM), and MMP-9 (K_i = 600 nM). This inhibitor appears to behave similarly to TIMP-1 and TIMP-2 in the slow-binding component of inhibition. Also exhibits a covalent mechanism-based behavior in inhibition of these enzymes. Binds directly to the catalytic zinc ion on MMP-2.	500 µg
MMP-2/MMP-9 Inhibitor V	**444285**	A cell-permeable sulfonamido analog of SB-3CT (Cat. No. 444274) that displays enhanced aqueous solubility and improved selectivity (K_i = 16 nM, 180 nM, and 900 nM for MMP-2, MMP-9, and MMP-14, respectively). Inhibits MMP-3, MMP-7, and MMP-1 only at much higher concentrations (K_i = 3.6 µM, 295 µM, and > 25 µM, respectively). Binds to the enzyme active site and acts as an irreversible inhibitor. Reported to potently suppress cell migration and invasion of HT1080 cells (80% inhibition at 2 µM and > 25% inhibition at 100 nM, respectively). Unlike the general MMP inhibitor GM6001 (Cat. No. 364205), this inhibitor does not block the activation of cellular pro-MMP-2 by MT1-MMP.	500 µg
MMP-3 Inhibitor I	**444218**	**(Ac-RCGVPD-NH_2; Stromelysin-1 Inhibitor)** Inhibits the matrix metalloproteinase MMP-3 (IC_{50} = 5 µM).	5 mg
MMP-3 Inhibitor II	**444225**	**[N-Isobutyl-N-(4-methoxyphenylsulfonyl)-glycylhydroxamic Acid; NNGH]** A potent and cell-permeable inhibitor of human MMP-3 (K_i = 130 nM).	5 mg
MMP-3 Inhibitor III	**444242**	**{N-[[(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl) amino]carbonyl]-L-phenylalanine}** A potent inhibitor of MMP-3 (K_i = 3.2 µM). Inhibits MMP-2 only at higher concentrations (K_i >200 µM).	2 mg
MMP-3 Inhibitor IV	**444243**	**{α-[[[(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)amino]carbonyl] amino] -N-(cyclohexylmethyl)-(S)-benzenepropanamide}** A potent inhibitor of MMP-3 (K_i = 810 nM). Inhibits MMP-2 only at higher concentrations (K_i >200 µM).	2 mg
MMP-3 Inhibitor V	**444260**	**(4-Dibenzofuran-2'-yl-4-hydroximino-butyric Acid)** A potent and competitive inhibitor of both human and rabbit MMP-3 catalytic domains (wild type and mutants) with K_i values in the low µM range. The functional groups, namely the oxime and the carboxyl, are shown to interact with the active site zinc.	5 mg
MMP-3 Inhibitor VII	**444280**	**{3-[4-(4-cyanophenyl)phenoxy]propanohydroxamic Acid}** A potent nonpeptide inhibitor of MMP-3 (stromelysin; IC_{50} = 25 nM against the catalytic domain).	1 mg
MMP-3 Inhibitor VIII	**444281**	**{N-Hydroxy-2(R)-{[(4-methoxyphenyl)sulfonyl]-[benzylamino]}-4-methylpentanamide}** A cell-permeable *p*-methoxysulfonamido D-leucine-containing hydroxamate compound that acts as a potent inhibitor of human MMP-3 (stromelysin; K_i = 23 nM) and murine macrophage metalloelastase (MME/MMP-12; IC_{50} = 13 nM). Binds to the MMP active site Zn^{2+}. Reported to inhibit the release of keratan sulfate and sulfated glycosaminoglycan due to MMP-3 in the knee joint by 65% after iv dosing (12.5 µg/Kg) in a rabbit acute cartilage degradation model.	5 mg
MMP-8 Inhibitor I	**444237**	**{(3R)-(+)-[2-(4-Methoxybenzenesulfonyl)-1,2,3,4-tetrahydroisoquinoline-3-hydroxamate]}** A potent and cell-permeable inhibitor of MMP-8 (IC_{50} = 4 nM).	1 mg
MMP-9 Inhibitor I	**444278**	A cell-permeable, potent, selective, and reversible MMP-9 Inhibitor (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

Matrix Metalloproteinase Inhibitors *continued*

Product	Cat. No.	Comments	Size
MMP-9/MMP-13 Inhibitor I	**444252**	**[N-Hydroxy-1-(4-methoxyphenyl)sulfonyl-4-(4-biphenylcarbonyl)piperazine-2-carboxamide]** A piperazine-based, cell-permeable, and highly 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
Myricetin	**476275**	**(3,3',4',5,5',7-Hexahydroxyflavone)** A cell-permeable flavanoid that displays anti-inflammatory, anti-diabetic and anti-cancer properties. Acts as a non-ATP competitive MEK1 inhibitor (IC_{50} i = 9.0 µM, 0.6 µM, 2.6 µM, 1.7 µM, 27.5 µM and 12.1 µM, respectively) and PI 3-Kα and PIM-1 (IC_{50} = 1.8 µM and 0.78 µM). Reported to inhibit the activities of phosphodiesterase 1-4 (IC_{50} 50 a-mediated NF-κB signaling (at 50 µM in ECV304 cells) and insulin-stimulated glucose transport (K_i = ~ 33.5 µM in rat adipocytes). Further, induce apoptosis in HL-60 leukemia cells with an IC_{50} of 43 µM.	25 mg
XG076	**682300**	**7-Aza-2-phenylbenzisothizol-3-one** An isothiazolone derivative that inhibits the activation of pro-MMPs but does not affect the activity of active MMPs. Causes dose-dependent inhibition of IL-1ß-induced breakdown of proteoglycan in a cartilage organ culture assay (IC_{50} = 4.4 µM).	5 mg

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**	An inhibitor of angiogenesis. Inhibits capillary morphogenesis completely and reversibly at approximately 130 µM. At low concentrations, acts as a potent and specific inhibitor of transmembrane Na^+ entry and Na^+,K^+-ATPase. Also acts as an inhibitor of urokinase-type plasminogen activator (uPA). Blocks smooth muscle responses to contractile stimuli and palytoxin-induced conductance in skeletal muscle. Reduces electrical potential across tubular epithelium. At higher concentrations, blocks the Na^+/H^+ exchange pathway.	100 mg
Plasminogen Activator Inhibitor-1, Human, Recombinant	**528205**	**(PAI-1)** PAI-1 is the primary inhibitor of both tissue plasminogen activator (tPA) and urokinase (uPA). PAI-1 can exist either in an active inhibitory conformation or in an inactive or latent conformation. This highly purified preparation has not been exposed to denaturing conditions and has been chromatographically purified of latent material. PAI-1 is a marker for acute myocardial infarction and several thrombolytic disorders. Protects platelets against the inhibitory effects of plasma. Reported to be an important prognostic factor in breast cancer patients. PAI-1 is highly stable when stored at or below pH 6.6.	50 µg
Plasminogen Activator Inhibitor-1, Mutant, Human, Recombinant	**528208**	**(PAI-1, Mutant)** 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**	**(PAI-1)** This inhibitor contains a single minor conservative amino acid substitution of Ile^{91} to 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 ($t_{1/2}$ = 8 to 9 hours at 25˚C, pH 7.4).	50 µg
Plasminogen Activator Inhibitor-1, Rat, Recombinant	**528214**	**(PAI-1)** Inhibits human uPA (K_i = 5.7 x 10^6 M^{-1} sec^{-1}). Stable when stored at or below pH 6.6.	50 µg
uPA Inhibitor II	**672152**	**[UK122; 4-((5-Oxo-2-phenyl-4(5H)-oxazolylidene)methyl) benzenecarboximidamide, trifluoroacetate]** A cell-permeable oxazolidinone-carboxamidine compound that acts as a potent, selective, and active-site targeting inhibitor of urokinase-type plasminogen activator (uPA; IC_{50} = 200 nM) with much reduced activity against trypsin, thrombin, tPA, and plasmin (38%, 8%, 5%, and 0% inhibition, respectively, with 100 µM UK122). Shown to effectively inhibit the migration and invasion (80% and 68% inhibition, respectively, with 100 µM UK122), but not proliferation, of uPA-expressing CFPAC-1 pancreatic cells.	5 mg

SELECTION GUIDE FOR THE USE OF SPECIALIZED PROTEASE INHIBITOR COCKTAILS

Product	Cat. No.	Recommended Application
Protease Inhibitor Cocktail Set I	**539131**	General use
Protease Inhibitor Cocktail Set I, Animal-Free	**535142**	General use (animal-free)
Protease Inhibitor Cocktail Set II	**539132**	Bacterial cell extracts
Protease Inhibitor Cocktail Set III, EDTA-Free	**539134**	Mammalian cells and tissue extracts, immobilized metal affinity chromatography
Protease Inhibitor Cocktail Set III, Animal-Free	**535140**	Mammalian cells and tissue extracts (animal-free)
Protease Inhibitor Cocktail Set IV	**539136**	Fungal and yeast cell extracts
Protease Inhibitor Cocktail Set V, EDTA Free	**539137**	Mammalian cells and tissue extracts
Protease Inhibitor Cocktail Set V, Animal-Free	**535141**	Mammalian cells and tissue extracts (animal-free)
Protease Inhibitor Cocktail Set VI	**539133**	Plant cell extracts
Protease Inhibitor Cocktail Set VII	**539138**	Purification of proteins containing His•Tag® sequences
Protease Inhibitor Cocktail Set VIII	**539129**	Broad range cysteine protease inhibition
Serine Protease Inhibitor Cocktail Set I	**565000**	Broad range serine protease inhibition

PROTEASE INHIBITOR COCKTAILS

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 indicated amount of inhibitors.

Cat. No. 539131 — 1 vial
10 vials

Protease Inhibitor	Cat. No.	1x Concentration	Target Protease
AEBSF, Hydrochloride	**101500**	500 µM	Serine Proteases
Aprotinin, Bovine Lung, Crystalline	**619370**	150 nM	Serine Proteases and Esterases
E-64 Protease Inhibitor	**324890**	1 µM	Cysteine Proteases
EDTA, Disodium	**324503**	500 µM	Metalloproteases
Leupeptin, Hemisulfate	**108975**	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

Protease Inhibitor	Cat. No.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	20 mM	Serine Proteases
Bestatin	**200484**	1.7 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	200 µM	Cysteine Proteases
EDTA, Disodium	**324503**	500 µM	Metalloproteases
Pepstatin A	**516481**	2 mM	Aspartic Proteases

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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, 5 set

Protease Inhibitor	Cat. No.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	100 mM	Serine Proteases
Aprotinin, Bovine Lung, Crystalline	**616370**	80 µM	Broad Spectrum, Serine Proteases
Bestatin	**200484**	5 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	1.5 mM	Cysteine Proteases
Leupeptin, Hemisulfate	**108975**	2 mM	Cysteine Proteases and Trypsin-like Proteases
Pepstatin A	**516481**	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 ml, 1 set

Protease Inhibitor	Cat. No.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	100 mM	Serine Proteases
E-64 Protease Inhibitor	**324890**	1.5 mM	Cysteine Proteases
Pepstatin A	**516481**	2 mM	Aspartic Proteases
o-Phenanthroline	**516705**	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 — 1 set, 10 vials

Protease Inhibitor	Cat. No.	1X Concentration	Target Protease
AEBSF, Hydrochloride	**101500**	500 µM	Serine Proteases
Aprotinin, Bovine Lung, Crystalline	**616370**	150 nM	Broad-Spectrum, Serine Proteases
E-64 Protease Inhibitor	**324890**	1 µM	Cysteine Proteases
Leupeptin, Hemisulfate	**108975**	1 µM	Cysteine Proteases and Trypsin-like Proteases

Protease Inhibitor Cocktail Set VI

A cocktail of six protease inhibitors with broad specificity for the inhibition of aspartic, cysteine, serine, and metalloproteases as well as aminopeptidases. This cocktail is recommended for use with plant cell extracts.

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

Protease Inhibitor	Cat. No.	Concentration in the Vial	Target Protease
AEBSF, Hydrochloride	**101500**	200 mM	Serine Proteases
Bestatin	**200484**	10 mM	Aminopeptidase B and Leucine Aminopeptidase
E-64 Protease Inhibitor	**324890**	3 mM	Cysteine Proteases
Leupeptin, Hemisulfate	**108975**	2 mM	Cysteine Proteases and Trypsin-like Proteases
o-Phenanthroline	**516705**	500 mM	Metalloproteases
Pepstatin A	**516481**	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. One ml is recommended for the inhibition of proteases in 10 g cells.

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

Protease Inhibitor	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	200 µM	Metalloendopeptidases

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.

Cat. No. 539129 — 1 ml
1 set (5 x 1 ml)

Protease Inhibitor	Cat. No.	Mol Wt.	Concentration in the Vial	Target Protease
ALLN	**208719**	383.5	1.56 mM	Calpain I/II, Cathepsin B, Cathepsin L, Cysteine Proteases
Cathepsin Inhibitor I	**219415**	475.5	500 µM	Cathepsin B, Cathepsin L, Cathepsin S, Papain
E-64 Protease Inhibitor	**324890**	357.4	1.5 mM	Cysteine Proteases

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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 to 8.0 inhibits 95-98% of protease activity. EDTA is also provided separately to inhibit metalloproteinases.

Cat. No. 539124 1 set

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

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. 616370), 20 µM Elastatinal (Cat. No. 324691), and 1 µM GGACK (Cat. No. 347436).

Cat. No. 565000 1 vial
5 vials

Protease Inhibitors

Product	Cat. No.	Comments	Size
Acetyl-Pepstatin	**110175**	**[Ac-Val-Val-(3S,4S)-Sta-Ala-(3S,4S)-Sta-OH]** An aspartyl protease inhibitor that acts as an effective inhibitor of HIV-1 proteinase (K_i = 20 nM at pH 4.7) and HIV-2 proteinase (K_i = 5 nM at pH 4.7). Acts as a substrate-analog inhibitor.	1 mg
AEBSF, Hydrochloride	**101500**	**[4-(2-Aminoethyl)benzenesulfonylfluoride, HCl]** Specific, irreversible inhibitor of serine proteases. Inhibits chymotrypsin, kallikrein, plasmin, thrombin, trypsin, and related thrombolytic enzymes. Stable, nontoxic alternative to PMSF (Cat. No.52332) and DFP (Cat. No.30967). A ß-secretase inhibitor that inhibits ß-amyloid peptide (Aß) production and enhances amyloid precursor protein ($sAPPU_\alpha$) secretion in several cell lines at millimolar concentrations. Use at the same molar concentrations (0.1 - 1.0 mM) as PMSF for most applications.	50 mg 100 mg 500 mg 1 g
ALLM	**208721**	**(Calpain Inhibitor II)** 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). Inhibits activation-induced programmed cell death and restores defective immune responses in HIV^+ donors. Blocks nitric oxide production by activated macrophages by interfering with transcription of the inducible nitric oxide synthase gene. A weak inhibitor of proteasome.	25 mg
ALLN	**208719**	**(Calpain Inhibitor I; LLNL; MG 101)** Cell-permeable 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). Inhibits neutral cysteine proteases and the proteasome (K_i = 6 µM). Modulates the processing of the ß-amyloid precursor protein (ßAPP) to ß-amyloid (Aß). Protects against neuronal damage caused by hypoxia and ischemia. Inhibits apoptosis in thymocytes and metamyelocytes. Also inhibits reovirus-induced apoptosis in L929 cells. Inhibits the proteolysis of IκB-α and IκB-ß by the ubiquitin-proteasome complex. Inhibits cell cycle progression at G_1/S and metaphase/anaphase in CHO cells by inhibiting cyclin B degradation. Also prevents nitric oxide production by activated macrophages by interfering with transcription of the inducible nitric oxide synthase gene. A 10 mM (5 mg/1.30 ml) solution of ALLN (Cat. No.208750) in DMSO is also available.	5 mg 25 mg
InSolution™ALLN	**208750**	**(Calpain Inhibitor I; LLNL; MG 101)** A 10 mM (5 mg /1.3 ml) solution of ALLN (Cat. No. 208719) in DMSO.	5 mg

Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
Amastatin, *Streptomyces* sp.	**129875**	**[(2S,3R)-3-Amino-2-hydroxy-5-methylhexanoyl-Val-Val-Asp-OH]** Non-toxic inhibitor of aminopeptidase A (K_i = 1 µM) and leucine aminopeptidase. Also acts as a slow-binding, competitive inhibitor of aminopeptidase M. Does not inhibit aminopeptidase B, chymotrypsin, elastase, papain, pepsin, thermolysin, or trypsin.	1 mg
ε-Amino-*n*-caproic Acid	**1381**	**(EACA)** Lysine analog that inhibits carboxypeptidase B. Promotes rapid dissociation of plasmin by inhibiting activation of plasminogen by streptokinase.	500 g
Aminopeptidase N Inhibitor	**164602**	**[APN/CD13 Inhibitor; 2',3-Dinitroflavone-8-acetic acid; 3-Nitro-2-(2-nitrophenyl)-4-oxo-4H-1-benzopyran-8-acetic acid)]** A dinitroflavone compound that acts as a selective, reversible, and competitive inhibitor of aminopeptidase N (APN/CD13; IC_{50} = 25 µM in U937 cells). Displays ~2-3 fold lower inhibition potency than Bestatin (Cat. No.200484), but is not cytotoxic. Does not induce apoptosis, and only weakly affects the activities of MMP-9, angiotensin converting enzyme, neural endopeptidase, γ-glutamyl transpeptidase, DPPIV, and cathepsin-G even at concentrations as high as 1 mM.	5 mg
α_1-Antichymotrypsin, Human Plasma	**178196**	**(α_1-Achy; α_1-1X-Glycoprotein; α_1-1X)** Acute-phase protein present at ~45 mg/100 ml in plasma. Specific inhibitor of chymotrypsin-like serine proteinases. Molecular weight ranges from 65,000-68,000 daltons.	100 µg 1 mg
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).	10 mg
Antipain, Hydrochloride	**178220**	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
α_2-Antiplasmin, Human Plasma	**178221**	**(Primary Plasmin Inhibitor; α_2-Protease Inhibitor)** A 452-amino acid glycoprotein present in plasma at about 70 µg/ml. Efficiently inhibits the plasminogen activator-induced lysis of fibrin clots. Forms a covalent complex with plasmin and inactivates it.	100 µg
Antithrombin III, Human Plasma	**169756**	**(ATIII; Factor Xa inhibitor; Heparin cofactor)** Single-chain glycoprotein present in normal serum at about 23 mg/100 ml. Principal physiological inhibitor of thrombin. Present at higher levels in plasma than in serum because it complexes with thrombin during coagulation. Functions by inhibiting proteolytic enzymes involved in blood coagulation and fibrinolysis, including Factor Xa, plasmin, thrombin, and trypsin. Potency is strongly enhanced by heparin.	1 mg
α_1-Antitrypsin, Human Plasma	**178251**	**(α_1-AT; 3.5S α_1-Glycoprotein; α_1-Proteinase Inhibitor)** A single polypeptide chain of 394 amino acids and three carbohydrate side chains linked to asparagine residues present at about 290 mg/100 ml in acute phase plasma. Serine protease inhibitor that also acts as a major physiological regulator of elastase. Inhibitor of neutrophil elastase, cathepsin G, and proteinase 3.	1 mg 5 mg
p-APMSF, Hydrochloride	**178281**	**(*p*-Amidinophenylmethylsulfonylfluoride, HCl)** Alternative to DFP and PMSF. An irreversible inhibitor of trypsin-like serine proteases. Inhibits trypsin and thrombin in equimolar concentration. Acts on C1r, C1s, Factor Xa, and plasmin, requiring a 5- to 10-fold excess for complete irreversible inhibition. Inhibitory activity is approximately 1000-fold greater than that of PMSF.	5 mg
Aprotinin, Bovine Lung, Crystalline	**616370**	**(Pancreatic Trypsin Inhibitor; Trypsin-Kallikrein Inhibitor)** A competitive and reversible inhibitor of esterases and proteases. Forms a tight complex with and blocks the active site of the enzymes. Inhibits a number of different proteases, including chymotrypsin, coagulation factors involved in the prephase of blood clotting, kallikrein (K_d = 1 x 10^{-7} M), plasmin (K_d = 2.3 x 10^{-10} M), tissue and leukocytic proteinases, and trypsin (K_d = 5 x 10^{-14} M). Does not inhibit Factor Xa and thrombin. It is relatively acid- and heat-stable. Useful as a serine protease inhibitor during purification of proteins and in studies of zymogen activation systems.	10 mg 20 mg 100 mg
Aprotinin, Bovine Lung, Solution	**616399**	**(Kallikrein Inactivator)** Competitive reversible inhibitor of proteolytic and esterolytic activity. A relatively heat- and acid-stable serine protease inhibitor. Forms a tight complex, blocking the active site of the enzyme. Effective at concentrations equimolar with protease. Inhibits several proteases, including coagulation factors in the prephase of blood clotting, tissue and leukocytic proteinases, chymotrypsin, trypsin (K_d = 5 x 10-14 M), plasmin (K_d = 2.3 x 10-10 M), and kallikrein (K_d = 1 x 10-7 M). Proteases not inhibited by aprotinin include Factor Xa, thrombin, pepsin, papain, and carboxypeptidases A and B. Useful in protein purification and for extending the life of cells in culture by preventing proteolytic damage.	100 KU 500 KU

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Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
Aprotinin, Bovine, Recombinant, *Nicotiana* sp., Animal-Free	**616371**	Recombinant, bovine aprotinin supplied without animal-derived components. Aprotinin is a competitive, reversible inhibitor of proteolytic and esterolytic activity. A relatively heat- and acid-stable serine protease inhibitor. Forms a tight complex, blocking the active site of the enzyme. Effective at concentrations equimolar with protease. Inhibits several proteases, including coagulation factors in the prephase of blood clotting, tissue and leukocytic proteinases, chymotrypsin, trypsin (K_d = 5 x 10^{-14} M), plasmin (K_d = 2.3 x 10^{-10} M), and kallikrein (K_d = 1 x 10^{-7} M). Proteases not inhibited by aprotinin include Factor Xa, thrombin, pepsin, papain, and carboxypeptidases A and B. Useful for protein purification and for extending the life of cells in culture by preventing proteolytic damage.	1 mg 5 mg 25 mg
Benzamidine, Hydrochloride	**199001**	Inhibitor of trypsin and trypsin-like enzymes. Inhibits Factor VII autoactivation.	5 g 25 g
Bestatin	**200484**	**{[(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoyl]-Leu}** Binds to cell surfaces and inhibits surface aminopeptidases, notably aminopeptidase B and leucine aminopeptidase. Also acts as a potent aminopeptidase N inhibitor. Activates macrophages and T lymphocytes. Has antitumor properties.	10 mg
Bestatin Methyl Ester	**200485**	**{(-)-N-[(2S, 3R)-3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine Methyl Ester}** 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. Also augments Fas- or TNF-α-induced apoptosis in solid tumor cell lines.	5 mg
CA-074	**205530**	**{Cathepsin B Inhibitor III; [L-3-*trans*-(Propylcarbamoyl) oxirane-2-carbonyl]-L-isoleucyl-L-proline}** An epoxysuccinyl peptide that acts as a potent, irreversible, and specific inhibitor of cathepsin B (IC_{50} = 2.24 nM for rat liver cathepsin B). Reduces ischemia-induced neuronal death. Exhibits lower membrane permeability when compared to CA-074 Me (Cat. No.205531).	1 mg
CA-074 Me	**205531**	**{Cathepsin B Inhibitor IV; [L-3-*trans*-(Propylcarbamoyl)oxirane-2-carbonyl]-L-isoleucyl-L-proline Methyl Ester}** A cell-permeable analog of CA-074 (Cat. No.205530) that acts as an irreversible inhibitor of intracellular cathepsin B. Reported to inhibit bone resorption in rodent models and shown to inhibit B16 melanoma cell invasion *in vitro*.	1 mg
Calpastatin, Human, Recombinant, Domain I	**208900**	Domain I of human calpastatin. Endogenous protease inhibitor that acts specifically on Calpain-1 (Cat. No.208712). Exhibits greater inhibitory potency than calpain inhibitors I and II.	1 mg
Calpeptin	**3340051**	**(Benzyloxycarbonylleucyl-norleucinal)** A cell-permeable calpain inhibitor (ID_{50} = 52 nM for calpain-1; ID_{50} = 34 nM for calpain-2; ID_{50} = 138 nM for papain). Inhibits the Ca^{2+}-stimulated cleavage of p35 to p25 by calpain. Modulates the processing of ß-amyloid precursor protein to ß-amyloid (Aß). Promotes neurite elongation in differentiating PC12 cells. Prevents Ca^{2+}-ionophore-induced degradation of actin binding protein and P_{235} in platelets. Inhibits myosin light chain phosphorylation in platelets stimulated by collagen, ionomycin, or thrombin. Inhibits the growth of estrogen receptor positive breast cancer cells.	5 mg 25 mg 100 mg
Cathepsin B Inhibitor I	**342000**	**(Cathepsin B, Inhibitor I; Z-FA-FMK)** A cell-permeable, irreversible cathepsin B inhibitor. Blocks LPS-induced production of IL-1α and IL-1ß. Suitable as a negative control for caspase-1 and caspase-2 inhibitors because it lacks an aspartic acid residue at the P1 position.	1 mg 5 mg
Cathepsin B Inhibitor II	**219385**	**(Ac-LVK-CHO)** A more active lysinal analog of Leupeptin (Cat. No.108975). A more potent inhibitor of cathepsin B (IC_{50} = 4 nM) compared to leupeptin (IC_{50} = 310 nM).	1 mg
Cathepsin G Inhibitor I	**219372**	A potent, selective, reversible, competitive, non-peptide inhibitor of cathepsin G [IC_{50} = 53 nM and K_i = 63 nM]. Weakly inhibits chymotrypsin (K_i = 1.5 µM) and poorly inhibits thrombin, factor Xa, factor IXa, plasmin, trypsin, tryptase, proteinase 3, and human leukocyte elastase (IC_{50} > 100 µM).	1 mg
Cathepsin Inhibitor I	**219415**	**(Z-FG-NHO-Bz)** Call-permeable cysteine protease inhibitor. 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 = 2.4 x 10^3 M^{-1} sec^{-1}).	1 mg
Cathepsin Inhibitor II	**219417**	**(Z-FG-NHO-BzME)** Cysteine protease inhibitor. 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 = 4.3 x 10^4 M^{-1} sec^{-1}), and papain (k_2/K_i = 1.8 x 10^3 M^{-1} sec^{-1}).	1 mg

Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cathepsin Inhibitor III	**219419**	**(Z-FG-NHO-BzOME)** Cysteine protease inhibitor. Selectively inhibits cathepsin B (k_2/K_i = 1 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 x 10^3 M^{-1} sec^{-1}).	1 mg
Cathepsin K Inhibitor I	**219377**	**[1,3-Bis(N-carbobenzoyloxy-L-leucyl)amino Acetone; 1,3-Bis(CBZ-Leu-NH)-2-propanone]** A cell-permeable, symmetrical bis(acylamino)ketone that acts as a potent, selective, and reversible inhibitor of cathepsin K ($K_{i,app}$ = 22 nM). Shown to bind to cathepsin K and span both the S- and S'-subsites. A poor inhibitor of papain ($K_{i,app}$ > 10 µM) but displays greater selectivity towards other proteases of the papain family ($K_{i,app}$ = 340 nM, 890 nM, and 1.3 µM for cathepsin L, cathepsin S, and cathepsin B respectively). Inhibits trypsin and chymotrypsin activities only at higher concentrations ($K_{i,app}$ ≥ 50 µM).	5 mg
Cathepsin K Inhibitor II	**219379**	**[1-(N-Benzyloxycarbonyl-leucyl)-5-(N-Boc-phenylalanyl-leucyl) carbohydrazide; Inhibitor Boc-I; Z-L-NHNHCONHNH-LF-Boc]** A cell-permeable peptidyl bis-carbohydrazide compound that acts as a potent, selective, and reversible inhibitor of cathepsin K ($K_{i,app}$ = 6 nM). Shown to completely block cathepsin K activity in primary human synovial fibroblast cultures at 1 µM. At higher concentrations, also inhibits the activities of cathepsin B and papain ($K_{i,app}$ = 510 nM, 1.2 µM, respectively). Does not significantly inhibit cathepsin L.	1 mg
Cathepsin K Inhibitor III	**219381**	**[1-(N-Benzyloxycarbonyl-leucyl)-5-(phenylalanyl-leucyl) carbohydrazide; Inhibitor I; Z-L-NHNHCONHNH-LF-NH_2]** A cell-permeable peptidyl bis-carbohydrazide compound that acts as a potent, selective, and 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). Completely blocks cathepsin K activity in primary human synovial fibroblast cultures at 1 µM.	1 mg
Cathepsin L Inhibitor I	**219421**	**(Z-FF-FMK)** A potent, cell-permeable, and irreversible inhibitor of Cathepsin L (Cat. No.219402).	1 mg
Cathepsin L Inhibitor II	**219426**	**(Z-FY-CHO)** A potent and selective inhibitor of Cathepsin L (Cat. No. 219402).	5 mg
Cathepsin L Inhibitor III	**219427**	**[Z-FY(t-Bu)-DMK]** An irreversible inhibitor of Cathepsin L (Cat. No.219402). About 10,000-fold more effective against cathepsin L than cathepsin S.	5 mg
Cathepsin L Inhibitor IV	**219433**	**(1-Naphthalenesulfonyl-IW-CHO)** A potent, cell-permeable, selective, and reversible 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 and prevents bone loss in ovariectomized mice (~50 mg/kg).	1 mg
Cathepsin L Inhibitor V	**219435**	**[Z-FY(O*t*Bu)-COCHO]** A slow, tight-binding, and reversible inhibitor of human cathepsin L (K_i = 600 pM). Exhibits about 360-fold greater selectivity for cathepsin L compared to cathepsin B (K_i = 214 nM).	1 mg
Cathepsin L Inhibitor VI	**219495**	**[N-(4-Biphenylacetyl)-S-methylcysteine-(D)-Arg-Phe-ß-phenethylamide; Compound 7]** An end protected tripeptide that acts as a highly selective, potent, and reversible inhibitor of human recombinant cathepsin-L (K_i = 19 nM). Resists proteolysis by cathepsin-L and mimics the mode of autoinhibition of procathepsin-L. Displays ~310- and ~210-fold greater selectivity for cathepsin-L over cathepsin-K (K_i = 5.9 µM, human recomb.) and cathepsin-B (K_i = 4.1 µM, human recomb.), respectively.	5 mg
Cathepsin S Inhibitor	**219393**	**(Z-FL-COCHO)** A slow, tight-binding reversible inhibitor of recombinant cathepsin S (K_i = 185 pM). Exhibits about 410-fold greater selectivity for cathepsin S compared to cathepsin B (K_i = 76 nM).	1 mg
Cathepsin/Subtilisin Inhibitor	**219420**	**(Boc-VF-NHO-Bz-*p*Cl)** 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**	**{[(S)-1-Carboxy-2-phenylethyl]-carbamoyl-α-[2-amidohexahydro-4(S)-pyrimidyl]-(S)-glycyl-[A = Leu; B = Val; or C = Ile]-phenylalaninal}** Contains chymostatin "A" as a major form. Protease inhibitor produced by actinomycetes. Specifically inhibits chymotrypsin (ID_{50} = 150 ng/ml), papain (ID_{50} = 7.5 µg/ml), and most cysteine proteases.	5 mg 10 mg 25 mg

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Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cystatin C, Human Urine	**240896**	**Post γ-globulin** A low molecular weight non-glycosylated basic protein of the cystatin superfamily of cysteine protease inhibitors that it is freely filtered by the glomerular membrane. Serum levels of cystatin C can be used as a specific and sensitive marker of glomerular filtration rate. Protects organisms against undesirable proteolysis by endogenous or exogenous enzymes. Thought to be linked to many disease processes including Alzheimer's disease, hereditary cerebral hemorrhage, and lung cancer.	50 µg
Cystatin, Egg White	**240891**	**(Ovocystatin)** Functions as a competitive and reversible inhibitor of cysteine- and/or thiol-proteases. Plays a protective and regulatory role. Inhibits papain and cathepsin B. Also inhibits legumain, a mammalian cysteine endopeptidase, with high potency (K_i < 5 nM).	500 µg
D-Val-Phe-Lys Chloromethyl Ketone, Dihydrochloride	**627624**	**(Plasmin Inhibitor, 2HCl)** Selective irreversible inhibitor of plasmin with high selectivity for plasmin (IC_{50} = 100 pM for human plasmin) over urokinase.	5 mg
1,5-Dansyl-Glu-Gly-Arg Chloromethyl Ketone, Dihydrochloride	**251700**	**(1,5-DNS-GGACK, 2HCl)** Effective irreversible inhibitor of uPA, Factor Xa, and urokinase. Fluorophore allows direct monitoring of interactions of labeled enzyme. Does not inhibit tPA.	5 mg
3,4-Dichloroisocoumarin	**287815**	A potent, irreversible inhibitor of serine proteases. Reacts with serine proteases to release an acylchloride moiety that can acylate another active site residue. Inhibits granzyme B and blocks apoptotic internucleosomal DNA cleavage in thymocytes without the involvement of endonucleases. Does not affect thiol proteases and metalloproteases. Does not exhibit any activity towards ß-lactamases.	10 mg
Diisopropylfluorophosphate	**30967**	**(DFP)** Serine protease inhibitor. A potent, irreversible inactivator of acetylcholinesterase that can cross the blood-brain barrier. Selectively blocks T cell receptor-triggered programmed cell death in murine T cell hybridoma and in activated peripheral T cells.	1 g
Dipeptidylpeptidase II Inhibitor	**317621**	**(Dab-Pip; L-2,4-Diaminobutyrylpiperidinamide; DPP II Inhibitor)** An aminoacylpiperidine compound that acts as a potent and highly specific inhibitor of dipeptidylpeptidase II (IC_{50} = 130 nM). Displays >7,700-fold selectivity for DPP II over DPP IV (IC_{50} >1 mM) from human seminal fluid.	10 mg
Dipeptidylpeptidase IV Inhibitor I	**416200**	**(Diprotin A)** A dipeptidylpeptidase IV (DPP IV) inhibitor that inhibits both endo- and exopeptidase activities of DPPIV.	5 mg
Dipeptidylpeptidase IV Inhibitor II	**317638**	A novel acylating inhibitor for the proline-specific peptidases dipeptidylpeptidase II and dipeptidylpeptidase IV. Acts as a potent reversible inhibitor of human placenta dipeptidylpeptidase II (K_i = 3.8 µM) and porcine kidney dipeptidylpeptidase IV (K_i = 1 µM). Combines the efficacy of aminoacyl pyrrolidides and the potential transacylating capability of diacylhydroxylamines.	1 mg
Dipeptidylpeptidase IV Inhibitor III	**317641**	**[DPP IV Inhibitor III; 1-(((1-(Hydroxymethyl)cyclopentyl) amino)acetyl)-2,5-cis-pyrrolidinedicarbonitrile, HCl]** An orally bioavailable dicyanopyrrolidine compound that acts as a slow-binding and active site-targeting inhibitor of DPP IV (IC_{50} = 106 nM using recombinant human DPP IV and 38, 69, 92, and 100 nM in inhibiting DPP IV activity in plasma from rat, human, monkey, and dog, respectively) with little activity against DPP II, DPP III, DPP VIII, DPP IX, FAP, or APP even at concentrations as high as 30 µM. Reported to lower blood DPP IV activity and augment GLP-1 response in dog and mouse *in vivo*.	5 mg
Dipeptidylpeptidase IV Inhibitor IV, K579	**317642**	**[DPP IV Inhibitor IV; (S)-1-(4-Methyl-1-(2-pyrimidinyl)-4-piperidylamino)acetyl-2-pyrrolidinecarbonitrile]** A cyanopyrrolidine compound that acts as a potent DPP IV inhibitor (IC_{50} = 3, 5, 8, and 8 nM in inhibiting rat, human, monkey, and canine DDP IV, respectively). Oral administration of K579 in rats *in vivo* has been shown to reduce blood DPP IV activity and augment GLP-1 and insulin response after glucose intake and significantly reduce plasma glucose concentration.	5 mg
DL-2-Mercaptomethyl-3-guanidinoethylthiopropanoic Acid	**445825**	**(Plummer's Inhibitor)** Potent reversible inhibitor of human plasma carboxypeptidase N (K_i = 2 nM). Inhibits hydrolysis of bradykinin.	100 mg
E-64 Protease Inhibitor	**324890**	Irreversible inhibitor of cysteine proteases. Interacts with the S_n subsites of proteases. Has no action on cysteine residues in other proteins. Inhibits activation-induced programmed cell death and restores defective immune responses in HIV^+ donors. Specific active site titrant.	1 mg 5 mg 25 mg
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 acts as an effective inhibitor of collagenase.	100 µg

Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
EDTA, Tetrasodium Salt	**34103**	**(Ethylenediaminetetraacetic Acid, 4Na)** Organic chelating agent used in ion exchange, metal chelation, antioxidation procedures, spectrophotometric titration, and other chemical procedures.	500 g
Elastase Inhibitor I	**324692**	**(Boc-AAA-NHO-Bz; PPE Inhibitor)** Serine protease inhibitor. Inhibits porcine pancreatic elastase (PPE; k_i = 128 M^{-1} sec^{-1}) and thermitase (k_i = 1.14 x 10^3 M^{-1} sec^{-1}).	1 mg
Elastase Inhibitor II	**324744**	**(HNE Inhibitor; MeOSuc-AAPA-CMK; MSACK)** A potent irreversible inhibitor of human neutrophil elastase (HNE). Inhibition results from cross-linking of the catalytic residues His^{57} and Ser^{195}.	5 mg
Elastase Inhibitor III	**324745**	**(HLE Inhibitor; MeOSuc-AAPV-CMK)** A potent irreversible inhibitor of human leukocyte elastase (HLE) (K_i = 10 µM). Protects against lung injury induced by instillation of elastase.	5 mg
Elastatinal	**324691**	An inhibitor of elastase-like serine protease produced by actinomycetes. Inhibits PMSF-stimulated degradation of histone H1 and HMG proteins. Also inhibits α_2-macroglobulin-protease complexes. *Inhibitory activity: ~0.5 µg/ml using Suc-$(Ala)_3$-pNA as a substrate at 25˚C, pH 8.0.*	5 mg
EST	**330005**	**[E-64d; (2S,3S)-*trans*-Epoxysuccinyl-L-leucylamido-3-methylbutane Ethyl Ester; Loxistatin]** A cell-permeable, irreversible inhibitor of cysteine proteases. Similar to E-64 (Cat. No.324890) but devoid of charged groups. Reported to inhibit calpain-1 activation. The inhibitory activity of EST has been attributed to E-64c, the free acid formed by hydrolysis of the ester *in vivo*. Used in animal models of muscular dystrophy.	1 mg
FUT-175	**344960**	**(6-Amidino-2-naphthyl-4-guanidinobenzoate Dimethanesulfonate; Futhan; Nafamostat Mesylate)** A synthetic broad-specificity serine protease inhibitor. Potently inhibits both coagulation and complement proteinases as well as Granzyme A. Also effective toward Hageman factor and Factor Xa at submicromolar concentrations.	5 mg
GGACK	**347436**	**(Glu-Gly-Arg-chloromethyl Ketone)** An irreversible inhibitor of urokinase (IC_{50} <1 µM) and Factor Xa.	5 mg
2-Guanidinoethyl-mercaptosuccinic Acid	**369334**	**(GEMSA)** 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**	**(Hexadecylsulfonyl Fluoride)** An active site-directed, serine-specific modifying agent that acts as an irreversible inhibitor of palmitoyl-protein thioesterase-1 (K_i = 125 µM). Inhibits lipase, but not phospholipase C activity in *Pseudomonas aeruginosa* culture supernatant and phospholipase A activity in *E. coli*. These lysosomal hydrolases are not affected by PMSF (Cat. No.52332).	25 mg 100 mg
Hirudin, *Hirudo medicinalis*, Recombinant, *Saccharomyces cerevisiae*	**377853**	HV1 form devoid of sulfate residue at Tyr^{63}. Has highly specific antithrombin properties. Inactivates thrombin by blocking substrate binding groups.	2000U
α-Iodoacetamide	**407710**	An irreversible inhibitor of several cysteine proteases. Useful for alkylating cysteine and methionine residues.	25 g
Iodoacetic Acid, Sodium Salt	**407719**	Inhibits cysteine proteases.	25 g
$(Z\text{-}LL)_2$Ketone	**421050**	**(1,3-di-(N-Carboxybenzoyl-L-leucyl-L-leucyl)amino Acetone)** A novel cysteine protease inhibitor that specifically and efficiently inhibits processing of the p-Prl signal peptide (IC_{50} = ~ 50 nM) without affecting the activities of signal peptidases and other proteases such as lysosomal cathepsins and proteasomes.	5 mg
Kininogen, High Molecular Weight, Single Chain, Human Plasma	**422686**	**(HMWK, Fitzgerald factor)** Native, single chain, high molecular weight Kininogen from human plasma. Nonenzymatic cofactor of the contact activation system. Links prekallikrein to negatively charged surfaces, thereby allowing activation to kallikrein by surface-bound Factor α-XIIa. Also circulates in plasma in complex with Factor XI and may play a role in the activation of Factor XI to Factor XIa by Factor α-XIIa. Serves as a source of bradykinin, a potent vasoactive peptide important in hypotension studies.	1 mg
Kininogen, High Molecular Weight, Two Chain, Human Plasma	**422688**	Native, two-chain, high molecular weight Kininogen from human plasma prepared by kallikrein digestion of kininogen, which is then repurified to remove traces of kallikrein. Binds to papain and cathepsin S with high affinity, exhibiting 2:1 binding stoichiometry.	1 mg
Leuhistin	**432077**	**[((2R,3S)-3-Amino-2-hydroxy-2-(1H-imidazol-4-ylmethyl)-5-methyl)-5-methylhexanoic Acid]** Microbial product. A competitive inhibitor of aminopeptidase M (K_i = 230 nM).	5 mg

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Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
Leupeptin, Hemisulfate	**108975**	**(Ac-LLR-CHO, ½H_2SO_4; Ac-Leu-Leu-Arginal)** A reversible inhibitor of trypsin-like proteases and cysteine proteases. Also known to inhibit activation-induced programmed cell death and to restore defective immune responses of HIV^+ donors.	5 mg 10 mg 25 mg 50 mg 100 mg
α_2-Macroglobulin, Human Plasma	**441251**	**(a_2M; a_2MG)** A multifunctional, secreted glycoprotein that acts as a broad range irreversible protease inhibitor that forms a "trap" around most proteases. α_2M is so large a molecule that it tends to remain intravascular. Localized on the surface of peripheral blood lymphocytes. Multifunctional activities include promoting growth of mammalian cells in culture, stimulating regeneration of lymphocytes in irradiated mice, transporting zinc, and acting as proteinase inhibitor that controls the clotting and fibrinolytic system.	1 mg 10 mg
Marimastat	**444289**	**(2S,3R)-N^4-((1S)-2,2-Dimethyl-1-((methylamino)carbonyl) propyl)-N^1,2-hydroxy-3-(2-methylpropyl)butanediamide** An orally active peptidyl hydroxamate-based broad-spectrum MMP inhibitor (IC_{50} in nM = 5, 6, 200, 20, 2, 1.8 and 3.8 for MMP-1, -2, -3, -7, -8, -14 and TACE, respectively) that targets both the substrate binding site and the active-site Zn^{2+}. Marimastate is widely used in studying the involvement of MMPs in various cellular and pathological processes both *in vitro* and *in vivo*.	5 mg
α_1-PDX, Human, Recombinant, *E. coli*	**126850**	**(α_1-Antitrypsin Portland)** Recombinant protein derived from the bioengineered human α_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). Extracellular application of α_1-PDX can be used to inhibit the processing of biologically significant proteins including viral envelope glycoproteins, bacterial toxins, receptors, and growth factors. Useful for *in vivo* and *in vitro* furin inhibition assays.	2.5 mg
Pepstatin A, Penetratin	**516483**	**(PepA-Antp$_{43-58}$; PepA-RQIKIWFQNRRMKWKK-OH)** A Pepstatin A (PepA; Cat. No.516481) penetratin (pAntp$_{43-58}$) conjugate (PepA-P) that is ~75% less potent against Cathespins D/E (IC_{50} = 920 nM) than PepA in cell-free assays, presumably due to its decreased solubility. However, with its enhanced permeability, PepA-P is much more active than PepA in inhibiting cellular aspartic protease activity in MCF7 (94.1% vs. 54.6% inhibition wtih 10 µM respective compound), Boleths, and Dendritic cultures. PepA-P, but not PepA, effectively interferes with antigen processing by primary APCs and the subsequent activation of antigen-specific memory T cells.	1 mg
Pepstatin A, Synthetic	**516481**	**(Isovaleryl-Val-Val-4-amino-3-hydroxy-6-methylheptanoyl-Ala-4-amino-3-hydroxy-6-methylheptanoic Acid; Iva-Val-Val-Sta-Ala-Sta)** A reversible inhibitor of aspartic proteases. Inhibits cathepsin D, pepsin, and renin. Reported to block apoptosis induced by CA-074 (Cat. No.205530) in PC12 cell lines.	5 mg 25 mg 100 mg
o-Phenanthroline	**516705**	**1,10-Phenanthroline Monohydrate** A metal chelating agent that prevents the induction of chromosomal aberrations in streptozotocin-treated cells. Acts as a metalloprotease inhibitor. Inhibits glioma invasion *in vitro*.	500 mg
Phenylmethylsulfonyl Fluoride	**52332**	**(Benzylsulfonyl Fluoride; PMSF)** Irreversible inhibitor of serine proteases. Its mechanism of action is analogous to that of diisopropylfluorophosphate. PMSF causes sulfonylation of the active-site serine residues. Also reported to inhibit internucleosomal DNA fragmentation in immature thymocytes. For a related, more stable inhibitor, see AEBSF (Cat. No.101500).	1 g 5 g 25 g
Phosphoramidon, Disodium Salt	**525276**	**[N-α-Rhamnopyranosyloxyhydroxyphosphinyl)-L-leucyl-L-tryptophan, 2Na]** Inhibits some metalloendopeptidases. Highly specific inhibitor of thermolysin. Inhibits the conversion of big endothelin-1 to endothelin (IC_{50} = 4.6 µM).	5 mg
PPACK Dihydrochloride, Biotinylated	**520224**	**(Biotin-X-D-Phe-Pro-Arg-chloromethylketone, 2HCl)** 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	**520222**	**(D-Phe-Pro-Arg-Chloro-methylketone, 2HCl)** Extremely potent and selective irreversible inhibitor of thrombin ($K_{obs}/[I] = 10^7 M^{-1}S^{-1}$). Reacts with thrombin in a 1:1 stoichiometry. Can also be used to inhibit tissue plasminogen activator, Factor VIIa, and Factor XIa.	5 mg 25 mg
PPACKII, Trifluoroacetate Salt	**520219**	Potent and specific irreversible inhibitor of plasma and glandular kallikreins.	10 mg

Protease Inhibitors *continued*

Product	Cat. No.	Comments	Size
Prolyl Endopeptidase Inhibitor II	**537011**	**(Z-PP-CHO)** 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, respectively). Reported to form a hemiacetal with the active site serine of the enzyme.	5 mg
Protease Arrest™ Reagent	**539124**	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. EDTA is also provided separately to inhibit metalloproteinases. Protease Arrest™ Reagent is provided as a 100X solution that when diluted in extraction buffer at pH 7.0-8.0 inhibits 95-98% of protease activity. Supplied with a data sheet.	1 set
Proteinase K Inhibitor	**539470**	**MeOSuc-AAPF-CMK** A tetrapeptidyl chloromethyl ketone compound that acts as an active-site-targeting irreversible inhibitor against proteinase K (Cat. Nos.539480,70663, and71049). Shown to be more potent than MeOSuc-AAPV-CMK (Cat. Nos.324745) in preventing the degradation of reverse transcriptase and albumin by proteinase K.	10 mg
TLCK, Hydrochloride	**616382**	**(N^{α}-Tosyl-Lys-Chloromethylketone, HCl)** Inhibits trypsin-like serine proteinases. Irreversibly inactivates trypsin without affecting chymotrypsin. Prevents nitric oxide production by activated macrophages by interfering with transcription of the iNOS gene. Blocks cell-cell adhesion and binding of HIV-1 virus to the target cells. In macrophages, blocks nitric oxide synthase induced by interferon-γ and lipopolysaccharides (EC_{50} = 80 µM). Prevents endonucleolysis accompanying apoptotic death of HL-60 leukemia cells and normal thymocytes.	50 mg 250 mg
TPCK	**616387**	**(N^{α}-Tosyl-Phe-Chloromethylketone)** Irreversible inhibitor of chymotrypsin. Useful for inhibiting chymotrypsin activity in trypsin preparations. Inhibits apoptosis in thymocytes. Blocks the induction of nitric oxide synthase by γ-interferon and lipopolysaccharides (EC_{50} = 20 µM).	250 mg 1 g
Trypsin Inhibitor, Corn	**650345**	Specific, reversible inhibitor of trypsin. Also inhibits human Factor XIIa. May function in host resistance against fungal pathogens in crops.	1 mg
Trypsin Inhibitor, Soybean	**65035**	A reversible inhibitor of trypsin that binds to trypsin in a stoichiometric, pH-dependent manner (K_d = 500 nM at pH 7.8).	100 mg 1 g
Trypsin Inhibitor, Soybean, High Activity	**650357**	Component VI of Rackis. Does not inhibit chymotrypsin activity.	100 mg 250 mg
uPA Inhibitor	**672151**	**(4-Iodo-benzo[b]thiophene-2-carboxamidine, HCl)** A cell-permeable carboxamidine compound that acts as a potent substrate-competitive inhibitor of uPA, trypsin, and tryptase (K_i = 0.32, 0.44, and 1.5 µM, respectively), with good selectivity relative to tPA, Thrombin, and Factor Xa (K_i = 16.8, 20, and 30 µM, respectively). Reported to block cell surface uPA-mediated, plasminogen-dependent, degradation of fibronectin by HT1080 cells in a dose-dependent manner (IC_{50} = 540 nM).	5 mg

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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. The 19S complex "caps" at each end of the 20S proteasome help in unfolding protein substrates. The 19S cap contains subunits with ATPase activity, subunits that recognize and bind polyubiquitin chains and putative unfoldases that unfold protein chains and translocate them into the 20S proteasome. 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 η-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 Pathway Inhibitors

Product	Cat. No.	Comments	Size
AdaAhX$_3$L$_3$VS	**114802**	A potent, covalent, cell-permeable, irreversible inhibitor of chymotrypsin-like (50-100 nM), trypsin-like (1-5 µM), and PGPH (0.5-1 µM) activities of the 20S proteasome.	250 µg
ALLN (Calpain Inhibitor I)	**208719**	Cell-permeable 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). Inhibits neutral cysteine proteases and the proteasome (K_i = 6 µM). Modulates the processing of the ß-amyloid precursor protein (ßAPP) to ß-amyloid (Aß). Protects against neuronal damage caused by hypoxia and ischemia. Inhibits apoptosis in thymocytes and metamyelocytes. Also inhibits reovirus-induced apoptosis in L929 cells. Inhibits the proteolysis of IκB-α and IκB-ß by the ubiquitin-proteasome complex. Inhibits cell cycle progression at G_1/S and metaphase/anaphase in CHO cells by inhibiting cyclin B degradation. Also prevents nitric oxide production by activated macrophages by interfering with transcription of the inducible nitric oxide synthase gene. A 10 mM (5 mg/1.30 ml) solution of ALLN (Cat. No.208750) in DMSO is also available.	5 mg 25 mg

Proteasome and Ubiquitination Pathway Inhibitors *continued*

Product	Cat. No.	Comments	Size
Celastrol, *Celastrus scandens*	**219465**	**3-Hydroxy-24-nor-2-oxo-1(10),3,5,7-friedelatetraen-29-oic Acid** A cell-permeable dienone-phenolic triterpene compound that exhibits antioxidant and anti-inflammatory properties. It suppresses LPS-induced pro-inflammatory cytokines release in macrophages and monocytes (IC_{50} = 40 nM for IL-1ß and IL-1α, 80 nM for IL-6, 110 nM for PGE_2, and 210 nM for IL-8 and TNF-α), as well as LPS-induced NF-κB activation (IC_{50} = 270 nM) and NO production (IC_{50} = 230 nM) in RAW264.7 cells. Preferentially inhibits chymotrypsin-like activity of 20S proteasome with an IC_{50} of 2.5 µM. Has also been shown to inhibit lipid peroxidation induced by ADP and Fe^{2+} in rat liver mitochondria (IC_{50} = 7 µM). Significantly improves the performance in memory, learning, and psychomotor activity in rats. May be useful to minimize inflammation in Alzheimer's disease (AD).	10 mg
Epoxomicin, Synthetic	**324800**	An antitumor and anti-inflammatory agent that acts as a potent, highly specific, and irreversible inhibitor of chymotrypsin-like (CT-L), trypsin-like (T-L), and peptidyl-glutamyl peptide hydrolyzing (PGPH) activities of the proteasome. Modifies the proteasomal catalytic subunits LMP-7, MECL1, and Z. Does not affect the activities of non-proteasomal proteases such as trypsin, cathepsin B, or chymotrypsin. A 1 mM (50 µg/90 µl) solution of Epoxomicin, Synthetic (Cat. No.324801) in DMSO is also available.	100 µg
InSolution™Epoxomicin, Synthetic	**324801**	A 1 mM (50 µg/90 µl) solution of Epoxomicin, Synthetic (Cat. No. 324800) in DMSO.	50 µg
Hdm2 E3 Ligase Inhibitor	**373225**	A cell-permeable and reversible inhibitor of Hdm2 E3 ligase that selectively blocks Hdm2 E3-mediated ubiquitination. Has been shown to inhibit ubiquitination of p53 *in vitro* (IC_{50} = 12.7 µM using Ub-Ubc as the donor substrate). Exhibits little effect towards other ubiquitin-using enzymes (IC_{50} > 100 µM for E1, Nedd-4, and SCF) or the auto-ubiquitination activity of Hdm2. The inhibition is non-competitive with respect to either the donor or acceptor substrate.	5 mg
Lactacystin, Synthetic	**426100**	An irreversible proteasome inhibitor. A *Streptomyces* metabolite that acts as a highly specific inhibitor of the 20S proteasome (MCP; multicatalytic proteinase complex). Blocks proteasome activity by targeting the catalytic ß-subunit. Acts as a covalent inhibitor of the chymotrypsin- and trypsin-like activities of the proteasome. Induces neurite outgrowth in Neuro 2A mouse neuroblastoma cells and inhibits progression of synchronized Neuro 2A cells and MG-63 human osteosarcoma cells beyond the G_1 phase of the cell cycle. Reported to induce apoptosis in human monoblast U937 cells. Also inhibits NF-κB activation (IC_{50} = 10 µM).	200 µg
clasto-Lactacystin-ß-lactone	**426102**	A highly specific, cell-permeable, and irreversible 20S proteasome inhibitor. It is believed that *in vitro*, the natural product Lactacystin (Cat. No.426100) acts as a precursor for *clasto*-lactacystin ß-lactone and that the latter is the sole species that interacts with the proteasome.	100 µg
α-Methylomuralide	**426104**	A cell-permeable α-methyl analog of *clasto*-Lactacystin ß-Lactone (Omuralide; Cat. No.426102) that displays improved hydrolytic stability. Reported to be a potent, selective, 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**	Potent reversible proteasome inhibitor (K_i = 21 nM and 35 nM for 20S and 26S proteasome, respectively). Specifically inhibits the chymotrypsin-like activity of the proteasome and induces apoptosis in Rat-1 and PC12 cells.	5 mg
InSolution™MG-132	**474791**	Supplied as a 10 mM (1 mg / 210 µl) solution of MG-132 (Cat. No. 474790) in anhydrous DMSO.	1 mg
MG-132 (Z-LLL-CHO)	**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. Activates c-Jun N-terminal kinase (JNK1), which initiates apoptosis. Inhibits NF-κB activation (IC_{50} = 3 µM). Prevents ß-secretase cleavage. A 10 mM (1 mg/210 µl) solution of MG-132 (Cat. No.474791) in DMSO is also available.	1 mg 5 mg
NP-LLL-VS	**492025**	An intermediate that can be used to prepare radiolabeled ^{125}I-NIP-L_3VS for proteasome inhibition studies.	500 µg
Proteasome Inhibitor I	**539160**	**(PSI)** A cell-permeable, reversible inhibitor of the chymotrypsin-like activity of the multicatalytic proteinase complex (MCP; 20S proteasome) in HT4 cells. Causes the accumulation of ubiquitinated proteins in neuronal cells. Prevents the activation of NF-κB in response to TNF-α and Okadaic Acid (Cat. No.495604) through inhibition of IκB-α degradation. A 50 mM (5 mg/162 µl) solution of Proteasome Inhibitor I (Cat. No.539161) in DMSO is also available.	1 mg 5 mg
InSolution™Proteasome Inhibitor I	**539161**	A 50 mM (5 mg/162 µl) solution of Proteasome Inhibitor I (Cat. No. 539160) in DMSO.	5 mg

Proteasome and Ubiquitination Pathway Inhibitors *continued*

Product	Cat. No.	Comments	Size
Proteasome Inhibitor II (Z-LLF-CHO)	**539162**	A potent, cell-permeable, and reversible proteasome inhibitor. Inhibits the chymotrypsin-like activity of the pituitary multicatalytic proteinase complex (MPC; K_i = 460 nM). Does not inhibit the peptidyl-glutamyl peptide hydrolyzing activity of MPC even at concentrations of 200 µM. Also blocks the decay of IκB-α and IκB-ß proteins in exponentially growing WEHI 231 cells.	1 mg 5 mg
Proteasome Inhibitor III [Z-LLL-B(OH)$_2$]	**539163**	A boronic acid-based, reversible proteasome inhibitor that is structurally similar to MG-132 (Cat. No.474790) but displays much higher potency (K_i = 30 pM vs. 4 nM for MG-132).	100 µg
Proteasome Inhibitor IV (Z-GPFL-CHO)	**539175**	A tetrapeptide aldehyde that acts as a highly selective and potent proteasomal inhibitor (K_i = 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 peptidyl-glutamyl peptide hydrolyzing activity). Shown to be a weak inhibitor of trypsin-like proteasomal activity.	5 mg
Proteasome Inhibitor IX, AM114	**539184**	**[3,5-bis-(4-Boronic acid-benzylidene)-1-methylpiperidin-4-one]** A cell-permeable boronate chalcone compound with ~ 30-fold higher potency than MG-132 (Cat. No.474790) in inhibiting 20S proteasome chymotrypsin-like activity (IC_{50} = ~ 1 µM). Blockage of proteasome degradation of cellular ubiquitinated p53 by AM114 has been attributed to its preferential apoptotic effect against p53-expressing cancer cells.	10 mg
Proteasome Inhibitor Set I	**539164**	Contains 1 mg of Proteasome Inhibitor I (Cat. No.539160), 200 µg of Lactacystin (Cat. No.426100), and 1 mg of MG-132 (Cat. No.474790). Supplied with a data sheet.	1 set
Proteasome Inhibitor Set II	**539165**	Contains 5 mg of ALLN (Cat. No.208719), 100 µg each of Epoxomicin (Cat. No.324800), and *clasto*-Lactacystin ß-Lactone (Cat. No.426102). Supplied with a data sheet.	1 set
Proteasome Inhibitor VII, Antiprotealide	**539179**	A cell-permeable, Omuralide-Salinosporamide hybrid that irreversibly inactivates the ß5-subunit of the human 20S proteasome. Shown to be ~2.5-fold more potent than Omuralide (Cat. No. 426102) and is expected to exhibit comparable whole cell potency as Salinosporamide A.	50 µg
Proteasome Inhibitor VIII, ß-Lactam 3	**539183**	**ß-Lactam 3** A ß-lactam analog of Proteasome Inhibitor VII, Antiprotealide (Cat. No. 539179) that acts as a selective and irreversible inhibitor of the 20S proteasome. While the rate of proteasome inhibition is slower than Omuralide (Cat. No. 426102), ß-lactam 3 displays prolonged aqueous stability and therefore may be better suited for biological evaluation.	100 µg
Ro106-9920	**557550**	A cell-permeable tetrazolopyridazine-phenylsulfoxide compound that displays anti-inflammatory properties. Acts as 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-1ß, and IL-6 inhibition) and rats. Does not inhibit $SCF^{\beta TRCP}$(IκBα ubiquitin ligase)-mediated ß-catenin ubiquitination in Jurkat cells. At 10 µM concentrations, also inhibits the activities of 5-lipoxygenase (by 89%) and EGFR kinase (by 63%).	1 mg 5 mg
Ro106-9920, Control	**557551**	A cell-permeable tetrazolopyridazine-phenylsulfide analog that serves as an inactive control (IκBαee ubiquitination IC_{50} > 80 µM) for Ro106-9920 (Cat. No.557550).	1 mg
Ubiquitin Aldehyde	**662056**	Potent and specific inhibitor of multiple ubiquitin hydrolases involved in pathways of intracellular protein modification and turnover. Useful for stabilizing endogenous or *in vitro* synthesized ubiquitin-protein conjugates. May also be used to enhance or decrease rates of ubiquitin-dependent degradation.	50 µg
Ubiquitin C-terminal Hydrolase-L1 Inhibitor II	**662088**	**3-Amino-2-benzoyl-6-oxo-6,7-dihydrothieno[2,3-b]pyridine-5-carboxylic acid** A thienopyridinone compound that inhibits UCH-L1-catalyzed substrate hydrolysis ($K_{i\,app}$ = 2.8 µM with Ub-AMC as the substrate) in an uncompetitive manner by targeting the enzyme-substrate complex, but not the free enzyme, while exhibiting little activity against UCH-L3, TGase 2, Papain, or Caspase-3 even at concentrations as high as 20 µM.	10 mg
Ubiquitin E1 Inhibitor	**662105**	**[Ubiquitin-Activating Enzyme E1 Inhibitor; PYR-41; 4-(4-(5-Nitro-furan-2-ylmethylene)-3,5-dioxo-pyrazolidin-1-yl)-benzoic acid ethyl ester, trihydrate]** A cell-permeable pyrazone compound that irreversibly (presumably via covalent modification) inhibits ubiquitin-activating enzyme E1 activity (IC_{50} <10 µM in cell-free E1 ubiquitination reactions), while exhibiting little or no activity against E3, E2, or caspase enzymatic activity. Blocks ubiquitination-dependent protein degradation and other ubiquitination-mediated cellular activities. E1 inactivation by PYR-41 or other means has been shown to result in an overall elevation of sumoylation.	25 mg

Proteasome and Ubiquitination Pathway Inhibitors *continued*

Product	Cat. No.	Comments	Size
Ubiquitin Isopeptidase Inhibitor I, G5	**662125**	**[NSC-144303; 3,5-bis((4-Nitrophenyl)methylene)-1,1-dioxide, tetrahydro-4H-thiopyran-4-one]** A cell-permeable cross-conjugated α,β-unsaturated dienone compound that induces caspase activation and apoptosis (IC_{50} = 1.76 and 1.6 µM in E1A and E1A/C9DN cells, respectively) via the apoptosome-independent mitochondrial pathway by selectively inhibiting ubiquitin isopeptidase activity (IC_{50} = ~ 30 µM). The cellular expression of Bax and Bak is essential for G5-activated apoptosis, while Bcl-2 appears to protect cells against the effect of G5. G5 is more potent than, but otherwise exhibits similar pharmacological effects as, Ubiquitin Isopeptidase Inhibitor II, F6 (Cat. No.662126). At higher concentrations (5-10 µM), shown to induce necrosis in apoptosis-resistant MEFs-DKO.	10 mg
Ubiquitin Isopeptidase Inhibitor II, F6	**662126**	**[NSC-632839; 3,5-bis((4-Methylphenyl)methylene)-1,1-dioxide, piperidin-4-one]** A cell-permeable cross-conjugated α,β-unsaturated dienone compound that induces caspase activation and apoptosis (IC_{50} = 15.65 and 16.23 µM in E1A and E1A/C9DN cells, respectively) via the apoptosome-independent mitochondrial pathway by selectively inhibiting ubiquitin isopeptidase activity. The cellular expression of Bax and Bak is essential for F6-activated apoptosis, while Bcl-2 appears to protect cells against the effect of F6.	10 mg
UCH-L1 Inhibitor	**662086**	An isatin O-acyl oxime compound that acts as a potent, reversible, competitive, and active site-directed inhibitor of UCH-L1 (K_i = 0.40 µM; IC_{50} = 0.88 µM) with ~28-fold greater selectivity over UCH-L3 (Cat. No.662090). Shown to increase proliferation of UCH-L1 expresssing tumor cell line SH-SY5Y at 5 µM. A useful tool for studying the roles of UCH-L1 in cancer, Parkinson's disease, and other neurological disorders. Permeability may vary from cell type to cell type.	10 mg
UCH-L3 Inhibitor	**662089**	A 1,3-indanedione compound that acts as a selective and potent inhibitor of UCH-L3 (IC_{50} = 0.6 µM) with ~125-fold greater selectivity over UCH-L1 (IC_{50} = 75 µM).	10 mg

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Tissue Inhibitors of Matrix Metalloproteinases (TIMPs)

Tissue inhibitors of metalloproteinases (TIMPs) are a family of ubiquitous, endogenous inhibitors that regulate the activation and activity of matrix metalloproteinases (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 (TACE). 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 (MMPs) implicated in the arthritic cartilage erosion.

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Tissue Inhibitors of Matrix Metalloproteinases

Product	Cat. No.	Comments	Size
TIMP-1, Human Neutrophil Granulocyte	**612080**	**(Tissue Inhibitor of Metalloproteinase-1)** Native TIMP-1 from human granulocyte. Member of a family of inhibitors that participate in the activation and regulation of MMP activity. Forms a non-covalent stoichiometric 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**	**(Tissue Inhibitor of Metalloproteinase-1)** Recombinant, human TIMP-1 expressed in CHO cells. Migrates as a 28 kDa protein under reducing conditions on SDS-PAGE.	3 µg
TIMP-2, Human Rheumatoid Synovial Fibroblast	**612084**	**(Tissue Inhibitor of Metalloproteinase-2)** Native TIMP-2 from human rheumatoid synovial fibroblast. Member of a family of inhibitors that participate in the activation and regulation of MMP activity. 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, Human, Recombinant	**PF021**	**(Tissue Inhibitor of Metalloproteinase 2)** Recombinant, human TIMP-2 expressed in CHC cells. Migrates as a 24 kDa protein under reducing conditions on SDS-PAGE. Use 20 µl per gel lane.	3 µg

ATPase Inhibitors

Product	Cat. No.	Comments	Size
Adenosine	**1160**	Induces apoptosis in human leukemia HL-60 cells. Has anti-arrhythmic properties.	10 g 100 g
Amiloride, Hydrochloride	**129876**	An inhibitor of angiogenesis. Inhibits capillary morphogenesis completely and reversibly at approximately 130 µM. At low concentrations, acts as a potent and specific inhibitor of transmembrane Na^+ entry and Na^+,K^+-ATPase. Also acts as an inhibitor of urokinase-type plasminogen activator (uPA). Blocks smooth muscle responses to contractile stimuli and palytoxin-induced conductance in skeletal muscle. Reduces electrical potential across tubular epithelium. At higher concentrations, blocks the Na^+/H^+ exchange pathway.	100 mg
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). A valuable tool for distinguishing among different types of ATPases. Blocks lysosomal cholesterol trafficking in macrophages and is known to interfere with pH regulation in brain cells. Exhibits cytotoxic effects on a number of cell lines in a cell viability assay. Reported to selectively inhibit ß-secretase, an enzyme involved in the processing of amyloid precursor protein (APP).	10 µg
BHQ	**286888**	**[*t*-BuBHQ; 2,5-Di-(*t*-butyl)-1,4-hydroquinone]** Mobilizes Ca^{2+} specifically from Ins(1,4,5)P_3-sensitive Ca^{2+} stores by inhibiting microsomal and sarcoplasmic reticulum Ca^{2+}-ATPase activity. Does not affect mitochondrial Ca^{2+} fluxes or plasma membrane Ca^{2+}/Mg^{2+} ATPase activity. Inhibits prostaglandin E_2 and prostacyclin formation in osteoblast-like cell lines.	100 mg
(±)-Blebbistatin	**203390**	A cell-permeable compound that acts as a selective, potent, and reversible inhibitor of nonmuscle myosin II. Inhibits the ATPase and gliding motility of human platelets (≤ 100 µM) without affecting myosin light chain kinase (MLCK) activity. Has been shown to block cell blebbing and to rapidly disrupt directed cell migration and cytokinesis in vertebrate cells. Does not disrupt mitosis or affect contractile ring assembly. A 50 mM (5 mg/342 µl) solution of (±)-Blebbistatin (Cat. No.203389) in 90% DMSO is also available.	5 mg
(–)-Blebbistatin	**203391**	The active enantiomer of (±)-Blebbistatin (Cat. No.203390) that accounts for the inhibitory activity towards ATPase (IC_{50} = ~ 2 µM) and myosin II-dependent cellular processes.	1 mg
(+)-Blebbistatin	**203392**	The inactive enantiomer of (±)-Blebbistatin (Cat. No.203390). Useful as a negative control for the active enantiomer (Cat. No.203391).	1 mg
InSolution™Blebbistatin, Racemic	**203389**	A 50 mM (5 mg/342 µl) solution of (±)-Blebbistatin (Cat. No. 203390) in DMSO.	5 mg
BTS	**203895**	**(N-Benzyl-*p*-toluenesulphonamide)** A potent inhibitor of Ca^{2+}-stimulated myosin S1 ATPase (IC_{50} = ~ 5 µM) and reversibly blocks the gliding motility. It also weakens myosin's interaction with F-actin. Much less effective in suppressing contraction in rat myocardial or rabbit slow twitch muscle and has no effect on platelet myosin II.	5 mg
Bufalin	**203900**	**[5ß, 20(22)-Bufadienolide-3ß, 14-diol]** A cardiotonic steroid isolated from toads of *Bufo* species that potently inhibits ouabain-sensitive Na^+,K^+-ATPase activity (IC_{50} = 1.4 nM). Induces apoptosis in various human cell lines such as leukemia HL-60 and U937 cells by altering the expression of apoptosis-related genes. Reported to stimulate the activities of p21 activated kinase (PAK) and c-Jun Kinase (JNK) in leukemic cell lines. Induces a transient increase in the expression of Tiam1 mRNA in U937 cell lines (~100 nM). Bufalin also down-regulates gene expression of the intracellular signaling protein 14-3-3 in rat lens, probably a consequence of Na^+,K^+-ATPase inhibition. Reduces the level of topoisomerase II in human leukemia cells.	10 mg
2,3-Butanedione 2-Monoxime	**203984**	**(BDM)** An inhibitor of skeletal and cardiac muscle contraction. A general reversible inhibitor of myosin ATPase in eukaryotes. A "chemical phosphatase," which dephosphorylates acetylcholinesterase poisoned with organophosphates. Inhibits Ca^{2+} currents in adult rat cervical ganglion in a reversible and dose-dependent manner (IC_{50} = 18.3 nM). Also shown to induce Ca^{2+} release from canine cardiac sarcoplasmic reticulum (SR).	500 mg
Calmidazolium Chloride	**208665**	**(Compound R 24571)** A cell-permeable calmodulin antagonist. At least 150 times more potent than Trifluoperazine (Cat. No.642150) as an inhibitor of brain calmodulin-dependent phosphodiesterase (IC_{50} = 10 nM). An inhibitor of voltage-gated Ca^{2+} channels. Stimulates the release of nitric oxide in neuroblastoma cells. Also acts as a strong non-competitive inhibitor of skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase (K_i = 60 nM). Known to prolong cardiac refractoriness *in vivo*.	10 mg
Cyclopiazonic Acid, *Penicillium cyclopium*	**239805**	**(CPA)** A cell-permeable, reversible inhibitor of sarcoplasmic reticulum Ca^{2+}-ATPase that releases Ca^{2+} from the same intracellular pools as Thapsigargin (Cat. No.586005). Inhibits Ca^{2+} uptake in cultured arterial smooth muscle cells (IC_{50} = 560 nM). Also known to inhibit sarcoplasmic reticular Ca^{2+}-ATPase that is distinct from actomyosin ATPase.	5 mg

ATPase Inhibitors *continued*

Product	Cat. No.	Comments	Size
DPC	**300265**	**(Diphenylamine-2-carboxylic Acid; 2,2'-Iminodibenzoic Acid; N-Phenylanthranilic Acid)** A potent, non-specific blocker of Cl^- channel and chloride-bicarbonate exchange. Also inhibits cystic fibrosis transmembrane regulator (CFTR) ATPase activity.	1 g
Eg5 Inhibitor III, Dimethylenastron	**324622**	**[7,7-Dimethyl-4-(3-hydroxyphenyl)-5-oxo-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-thione]** A cell-permeable quinazoline-thione compound that acts as a potent, specific, and reversible inhibitor of the microtubule-stimulated ATPase activity of the mitotic motor, Eg5 (IC_{50} = 200 nM). Exhibits little effect on the ATPase activity of kinesin-1, -4, -7 and -10 and is ~100-fold more potent than Monastrol (Cat. No.475879). Also inhibits bipolar spindle formation in both HeLa cells and in *Xenopus* egg extracts and induces cell cycle arrest (~1 µM). Shown to induce mitotic arrest and apoptosis and upregulate Hsp70 in human multiple myeloma cells.	1 mg 5 mg
Eg5 Inhibitor IV, VS-83	**324623**	**[5-Fluoro-3,4-dihydro-4(3'-hydroxyphenyl)quinazoline-2(1H)-thione]** A cell-permeable Monastrol (Cat. No.475879) analog with much enhanced potency and selectivity (over 8 other kinesins) in inhibiting mitotic kinesin Eg5-ATPase activity (IC_{50} = 1.17 vs. 20.73 µM for VS-83 and Monastrol, respectively) and in inducing monoasters formation (EC_{50} = 7.27 vs. 58.74 µM for BSC-1 cells treated with VS-83 and Monastrol, respectively). Shown to exhibit ≥10-fold antiproliferative activity than Monastrol against U-87 MG, U-118 MG, and U-373 MG glioblastoma cells.	5 mg
Eg5 Inhibitor V, trans-24	**324624**	**{(5R,11aS)-2-Benzyl-5-(3-hydroxyphenyl)-6H-1,2,3,5,11,11a-hexahydro-imidazo[1,5-b]-ß-carboline-1,3-dione}** A cell-permeable HR22C16 (Cat. No.385861) derivative that exhibits much enhanced potency against mitotic kinesin Eg5-ATPase activity (IC_{50} = 0.65 vs. 4.3 µM for *trans*-24 and HR22C16, respectively) and little or no activity against 9 other kinesins. Shown to induce monoastral phenotype in HeLa cells (20 µM).	5 mg
Eg5 Inhibitor VI	**324629**	**[KSP Inhibitor VI; N-(4'-(Trifluoromethyl)-4-biphenyl)sulfamide]** A cell-permeable biphenylsulfamide compound that acts as a potent, reversible, and ATP-competitive inhibitor of Eg5/KSP ATPase activity (IC_{50} = 18 nM) with reactivity against both wild-type and the D130V mutant (K_i = 6.2 nM and 7 nM, respectively) in cell-free assays. Due to a higher ATP binding affinity of the WT enzyme, the inhibitor exhibits a much weaker antiproliferative activity against WT-expressing cells in cultures (IC_{50} = 5.4 and 403 nM, using HCT116 D130V and HCT116, respectively) and its *in vivo* antitumor efficacy has only been demonstrated in HCT116 D130V xenografed mice, but not mice with WT KSP-bearing Colo205.	5 mg
Eg5 Inhibitor VII	**324631**	**[GSK-1; KSP Inhibitor VII; 6-(4-Trifluoromethyl) phenyl)-3,4-dihydro-2(1H)-quinolinone]** A cell-permeable quinolinone compound that acts as a highly potent and selective Eg5/KSP inhibitor (K_i = 1.4, 2.1, 2.2, and 1.7 nM for the mutant A133D, KHC-L5, D130V, and the wild-type KSP, respectively) by antagonizing ATP binding via an allosteric site. Effectively induces monopolar spindles in ovarian adenocarcinoma SKOV3 cells and inhibits the proliferation of colorectal carcinoma HCT116 cells (IC_{50} = 36 and 0.5 nM againt the parental and the ispinesib-resistant D130V mutant line, respectively). It is uncompetitive with respect to microtubule and exhibits little activity against a panel of 7 other mitotic kinesins.	5 mg
Folimycin, *Streptomyces* sp.	**344085**	**(Concanamycin A)** A highly sensitive and specific inhibitor of vacuolar-type H^+-ATPase (V-type; K_i = 20 pM). Inhibits acidification of organelles, such as lysosomes and the Golgi apparatus. Also blocks cell surface expression of viral envelope glycoproteins without affecting their synthesis. Useful for studies of intracellular protein translocation. Exhibits cytotoxic effects on a number of cell lines in a cell viability assay.	10 µg
Fumitremorgin C, *Aspergillus. Fumigatus*	**344847**	**NSC719655** A cell-permeable indolyldiketopiperazinyl mycotoxin that inhibits BCRP/ABCG2 (breast cancer resistance protein/ATP-binding cassette G2) multidrug transport activity. Also acts as a potent and specific chemosenzitizing agent.	250 µg
4-Hydroxynonenal	**393204**	**(HNE; 4-Hydroxy-2-nonenal)** A major aldehyde product formed by peroxidation of ω-6-unsaturated fatty acids that is regarded as a specific marker of lipid peroxidation. Inhibits proliferation and induces differentiation of HL-60 human leukemic cells. Also induces cell death in murine alveolar macrophages and in PC12 cells. An inhibitor of state 3 respiration at micromolar levels. Causes a transient increase in cytosolic Ca^{2+} and irreversibly inhibits Na^+, K^+-ATPase activity (IC_{50} = 120 µM). Acts as a reversible inhibitor of c-Jun N-terminal kinase (JNK).	1 mg

ATPase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Mastoparan	**444898**	**(INLKALAALAKKIL)** A cell-permeable synthetic peptide with sequence identical to *Vespula lewisii*. Amphiphilic wasp venom tetradecapeptide capable of directly activating pertussis toxin-sensitive G-proteins by a mechanism analogous to that of G-protein-coupled receptors. Acts preferentially on G_i and G_o rather than G_s. Potent facilitator of the mitochondrial permeability transition pore that is reported to induce apoptosis in cultured cerebellar granule neurons by causing a dramatic increase in intracellular Ca^{2+}. Acts as a calmodulin antagonist and activates phospholipase A_2. Causes a transient Ca^{2+} release from the sarcoplasmic reticulum. Also reported to inhibit Na^+,K^+-ATPase activity (IC_{50} = 7.5 µM).	1 mg
N-Ethylmaleimide	**34115**	**(NEM)** Sulfhydryl alkylating reagent that inhibits H^+-ATPase and suppresses the short circuit current (IC_{50} = 22 µM) in pancreatic duct cells. Inactivates NADP-dependent isocitrate dehydrogenase. Also a potent inhibitor of both Mg^{2+} and Ca^{2+}/Mg^{2+}-stimulated DNA fragmentation in rat liver nuclei. Stimulates arachidonic acid release through activation of PLA_2 in endothelial cells.	5 g
Oligomycin	**495455**	A mixture of A, B, and C isomers. A macrolide antibiotic that inhibits membrane-bound mitochondrial ATPase (F_1), preventing phosphoryl group transfer. Induces apoptosis in cultured human lymphoblastoid and other mammalian cells.	10 mg
Omeprazole	**496100**	**{H 168/68; 5-Methoxy-2[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole}** A cell-permeable pyridyl methylsulfinyl benzimidazole compound that acts as selective proton pump inhibitor. Behaves as a prodrug by undergoing an acid-catalyzed rearrangement to a thiol-reactive cationic sulfenamide that inhibits (H^+, K^+)-ATPase in the gastric milieu. An aryl hydrocarbon-like inducer of cytochrome P450 secretion in human liver.	50 mg
Ouabain, Octahydrate	**4995**	**(Strophanthin G)** Inhibits Na^+,K^+-ATPase. Exhibits cardiotonic properties. Preferentially enhances radiotoxicity in tumor cells and induces apoptosis by prolonging the irradiation-induced G_2 delay.	1 g
Phorbol-12,13-dibutyrate	**524390**	**(PDBu)** Strong irritant for mouse skin, but only moderately active as a tumor promoter. Activates protein kinase C. Stimulates the phosphorylation of Na^+,K^+- ATPase, thereby inhibiting its activity. Promotes the expression of inducible NOS in cultured hepatocytes. Commonly used in binding studies or in applications requiring high concentrations of phorbol compounds.	1 mg 5 mg
Suramin, Sodium Salt	**574625**	A reversible and competitive inhibitor of protein tyrosine phosphatases. An anti-neoplastic, anti-angiogenic agent that uncouples G-proteins from receptors presumably by blocking their interaction with intracellular receptor domains. Inhibits GDP-GTP exchange, the rate limiting step in the activation of G_α-subunits. A competitive inhibitor of reverse transcriptase. Reported to inhibit topoisomerases I and II. Inhibits Ca^{2+}-ATPase in sarcoplasmic reticulum membranes. Also inhibits the cell-surface binding of various growth factors, including EGF, PDGF, and TGF-ß. An inhibitor of phospholipase D (IC_{50} = 15 µM). Reported to interact with ATP-binding enzymes and P_2-purinergic receptors. An effective inhibitor of angiogenesis in the calmodulin assay when given in combination with angiostatic steroids.	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). Does not increase inositol phosphates and has no significant effect on protein kinase C. Increases Ca^{2+}-dependent Na^+ influx in human platelets in a dose-dependent manner. Induces apoptosis in rat thymocytes and in human hepatoma cells.	1 mg

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GTPase Inhibitors

Product	Cat. No.	Comments	Size
Dynamin Inhibitor I, Dynasore	**324410**	**[Sore to Dynamin; 3-Hydroxynaphthalene-2-carboxylic acid-(3,4-dihydroxybenzylidene)-hydrazide]** A cell-permeable semicarbazone compound that inhibits the GTPase activity of dynamin1/2 (IC_{50} ~15 µM) and Drp1, while exhibiting no significant effect against two other small GTPases, MxA and Cdc42. Dynasore has been used to elucidate the roles of dynamin in endocytosis mediated by both clathrin-coated and synaptic vesicles. The inhibitition is noncompetitive with respect to GTP and the inhibitor target site presumably resides in the GTPase domain. Shown to inhibit removal of both wt and ΔF508-CFTR from the plasma membrane.	10 mg
Dynamin Inhibitor II, MiTMAB	**324411**	**(TTAB; Myristyltrimethylammonium Bromide; Tetradecyltrimethylammonium Bromide)** A cell-permeable cationic surfactant that reversibly inhibits dynamin GTPase activity (IC_{50} = 3.15 µM) by targeting the PH domain and interfering with phospholipid binding. Shown to block dynamin I-dependent SVE (synaptic vesicle endocytosis) in rat brain synaptosomes and dynamin II-dependent RME (receptor-mediated endocytosis) in non-neuronal HeLa, A431, and COS-7 cells. Inhibition is competitive with respect to PS and noncompetitive with respect to GTP.	500 mg

NF-κB Activation Inhibitors

NF-κB, a eukaryotic transcription factor plays an important role in inflammation, autoimmune response, cell proliferation, and apoptosis by regulating the expression of genes involved in these processes. It 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, IκBη, 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 antitumor agents to block NF-κB activity or to increase sensitivity to conventional chemotherapy may have great therapeutic value.

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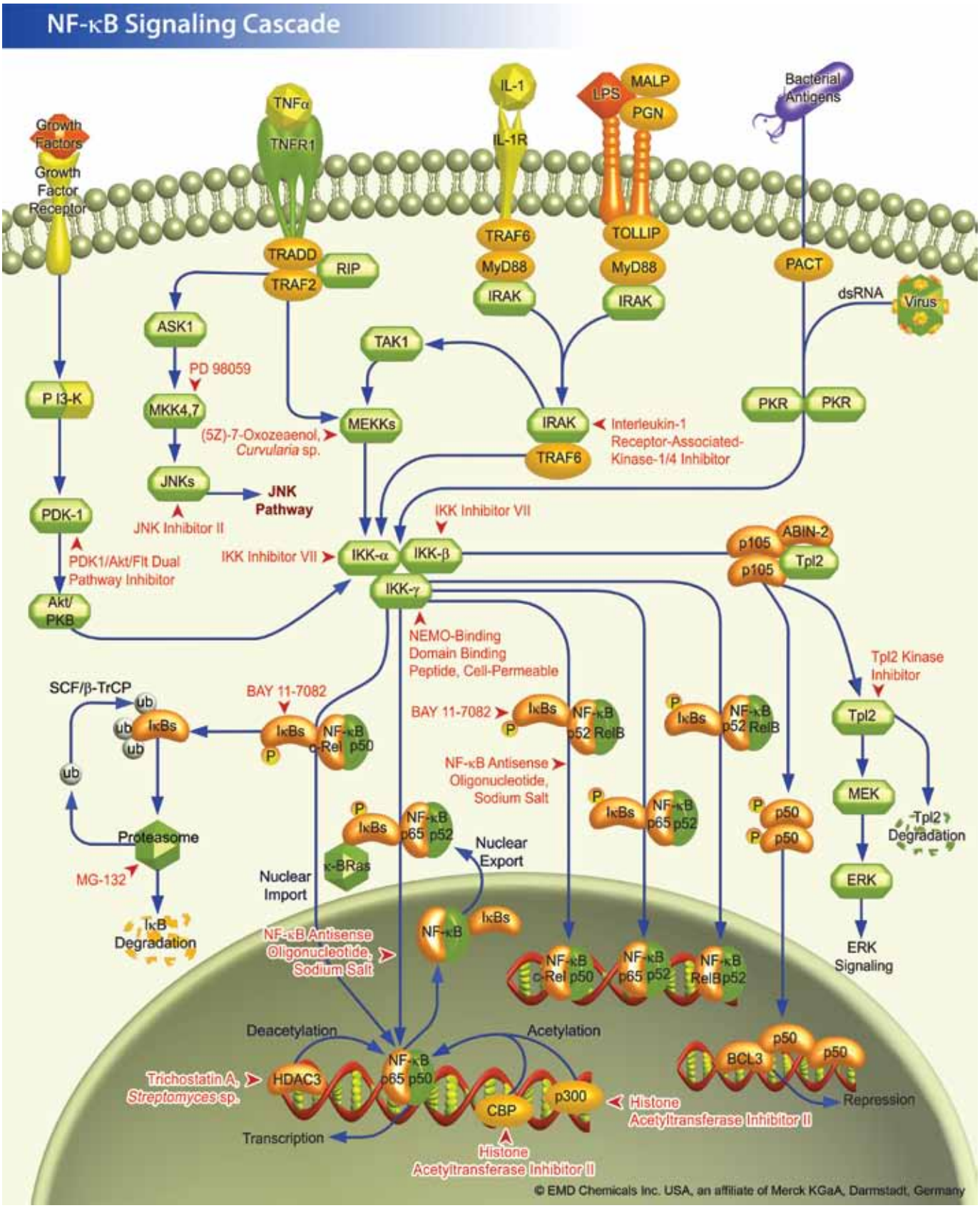
Highlighted below are inhibitors included in InhibitorSelect™ NFκB Signaling Pathway Inhibitor Panel (Cat. No. 481487). See page 184 or 204 for details.



NF-κB Activation Inhibitors

Product	Cat. No.	Comments	Size
Andrographolide	**172060**	A bicyclic diterpenoid lactone that displays anti-viral, anti-inflammatory, anti-apoptotic, and anti-hyperglycemic properties. Acts as an irreversible antagonist of NF-κB and AP-1 ($IC_{50} \leq 15$ µM) activation, and prevents *in vitro* and *in vivo* T cell activation. Exerts no effect on IκBα degradation, p50 and p65 nuclear translocation. Inhibits iNOS and Mac-1 expressions and ROS production, and prevents endotoxin shock in mouse model. Further, reported to activate PI 3K/Akt pathway.	50 mg
Aurothiomalate, Sodium Salt	**189401**	**Aurothiomalate, Sodium Salt** A gold(I) compound that inhibits the activity of IKK (ID_{50} = 10.9 µM) and disrupts PB1 (Phox and Bem1p) domain-mediated interactions between Par6 and PKCι (IC_{50} = ~ 1 µM) by modifying cysteine residues within the catalytic domain of IKK and the PB1 domain of PKCι. Inhibits PKCι-dependent Rac1 activation in A549 cells.	50 mg
BAY 11-7082	**196870**	**{(E)3-[(4-Methylphenyl)sulfonyl]-2-propenenitrile}** Potential anti-inflammatory agent that selectively and irreversibly inhibits the TNF-α-inducible phosphorylation of IκBα (IC_{50} = 10 µM), resulting in a decreased expression of NF-κB and of adhesion molecules. Does not affect constitutive IκBα autophosphorylation. Inhibits TNF-α-induced surface expression of the endothelial-leukocyte cell adhesion molecules E-selectin, VCAM-1, and ICAM-1. A 100 mM (10 mg/483 µl) solution of BAY 11-7082 (Cat. No.196871) in DMSO is also available is also available.	10 mg
InSolution™BAY 11-7082	**196871**	A 100 mM (10 mg/483 µl) solution of BAY 11-7082 (Cat. No. 196870) in DMSO.	10 mg
BAY 11-7085	**196872**	**{(E)3-[(4-*t*-Butylphenyl)sulfonyl]-2-propenenitrile}** Has biological properties very similar to those of BAY 11-7082 (Cat. No.196870). In addition, BAY 11-7085 shows potent anti-inflammatory properties *in vivo*.	10 mg
CAPE	**211200**	**(Caffeic Acid Phenethyl Ester, Synthetic)** A cell-permeable active component of propolis from honeybee hives. Known to have antiviral, anti-inflammatory, and immunomodulatory properties. Has also recently been shown to act as a potent and specific inhibitor of NF-κB activation. An inhibitor of HIV-1 integrase activity. Inhibits the growth of different types of transformed cells. Has been reported to suppress lipid peroxidation. Inhibits ornithine decarboxylase, protein tyrosine kinase (PTK), and lipoxygenase activities. Also induces apoptosis in cloned rat embryo fibroblast (CREF) cells transformed by a number of different oncogenes.	25 mg
(E)-Capsaicin	**211274**	**{[(E)-N-(4-Hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonenamide}** An active constituent of cayenne pepper with excitatory and desensitizing effects on a subset of primary afferent sensory neurons. An antagonist of acetylcholine-induced responses in rat PC12 cells. Exhibits anti-nociceptive and anti-inflammatory effects. Inhibits NF-κB activation by TNF. Reversibly inhibits platelet aggregation.	100 mg
Evodiamine, *Evodia rutaecarpa*	**341211**	A cell-permeable quinazolinocarboline alkaloid that displays antiproliferative, antimetastatic, apoptotic, vasorelaxant and vanilloid receptor agonist activities. Suppresses both inducible (≤ 250 nM in KBM-5, H1299, A293 and Jurkat T cells stimulated with 0.1 nM of TNF) and constitutive (> 500 nM in FaDU and U266 cells) NF-κB activation and NF-κB-regulated gene expression by inhibiting IκBα kinase (IKK) activation. Further, shown to selectively abrogate TNF-induced Akt activation and its association with IKK with no effects on JNK and p38MAPK activation, and promote the phosphorylations of Raf-1 kinase and Bcl-2.	5 mg
Gliotoxin, *Gladiocladium fimbriatum*	**371715**	**{2,3,5a,6-Tetrahydro-6-hydroxy-3(hyroxymethyl)-2-methyl-10H-3a,10a-epidithio-pyrazinol[1,2α]indole-1,4-dione}** An immunosuppressive secondary metabolite produced by several pathogenic fungi. Immunosuppressive effects are caused by blocking of membrane thiol groups. Causes apoptotic cell death in a variety of cell types including macrophages and thymocytes. Farnesyltransferase (FTase) inhibitor (IC_{50} = 1.1 µM). Reported to increase ryanodine Ca^{2+} channel activity possibly by oxidizing cysteine residues located on the ryanodine receptor. Specifically inhibits NF-κB activation in B and T cells at nanomolar concentrations.	1 mg
Helenalin, *Hypericum perforatum L.*	**374001**	**[Ambrosa-2,11(13)-dien-12-oic acid, 6-α,8-ß-dihydroxy-4-oxo-, 12,8-lactone]** A cell-permeable anti-inflammatory sesquiterpene lactone that acts as a specific NF-κB-DNA binding inhibitor by irreversibly alkylating free sulfhydryls of the cysteine residues on the p65 subunit. Exhibits no effect against the DNA-binding activity of the homodimer of p50 subunit, nor does it affect cellular NF-κB activation/nuclear translocation or IκB dissociation/degradation. An excellent research tool for studying NF-κB-mediated biological processes both in cultures *in vitro* and in animals *in vivo*.	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 preventing NF-κB activation. Also inhibits the production of nitric oxide by IL-1ß or IL-17 stimulated normal human chondrocytes. Reported to neither affect the synthesis of prostaglandin nor inhibit the activities of JNK and p38MAPK.	1 mg

NF-κB Activation Inhibitors *continued*

Product	Cat. No.	Comments	Size
IκB Kinase Inactive Control Peptide, Cell-Permeable	**401478**	**(Ac-AAVALLPAVLLALLAPDDRHDAGLDAMKDE-NH_2)** An inactive control for IκB Kinase Inhibitor Peptide (Cat. No.401477). A 14-amino acid peptide corresponding to the mutated recognition sequence of IκB (Ser^{32}→Ala and Ser^{36}→Ala) fused 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
IκB Kinase Inhibitor Peptide, Cell-Permeable	**401477**	**(Ac-AAVALLPAVLLALLAPDDRHDSGLDSMKDE-NH_2)** A 14-amino acid peptide corresponding to the active IκB phosphorylation recognition sequence fused 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 (kB activation. *Supplied as a trifluoroacetate salt.*	1 mg
IKK Inhibitor II, Wedelolactone	**401474**	**(7-Methoxy-5,11,12-trihydroxy-coumestan; Wedelolactone,** *Eclipta alba***)** The naturally isolated active ingredient of the herbal medicine, *Eclipta alba*, that acts as a cell permeable, selective and irreversible inhibitor of IKKα and ß kinase activity (IC_{50} kB-mediated gene transcription in cells by blocking the phosphorylation and degradation of IκBα. Has no effects on p38 MAP kinase or Akt.	1 mg
IKK Inhibitor III, BMS-345541	**401480**	**{4-(2'-Aminoethyl)amino-1,8-dimethylimidazo[1,2-a]quinoxaline, HCl}** A cell-permeable quinoxaline compound that displays anti-inflammatory properties. Acts as a 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) and no activity towards IKK and a panel of more than 15 unrelated protein kinases even at concentrations as high as 100 µM. Inhibits cellular IκBα phosphorylation (IC_{50} = 4 µM in THP-1 cells) and LPS-induced cytokine production both *in vitro* (IC_{50} = 1-5 µM in THP-1 cells) and *in vivo* (IC_{50} = 10 mg/kg in mice). Effectively blocks inflammation and joint destruction in a murine arthritis model.	1 mg
IKK Inhibitor VII	**401486**	A cell-permeable benzamido-pyrimidine compound that acts as a potent, selective, and ATP-competitive inhibitor of IKK (IC_{50} = 40 nM, 70 nM, and 200 nM for IKK-2, IKK complex, and IKK-1, respectively). Inhibits cellular IκBα degradation and NF-κB-mediated gene expression *in vitro* in HUVEC cells and has been shown to exhibit excellent *in vivo* efficacy both in mice and rats.	1 mg
IKK Inhibitor X	**401489**	**[N-(6-Chloro-9H-ß-carbolin-8-yl)nicotinamide]** A cell-permeable ß-carboline compound that displays anti-inflammatory properties. Acts as a potent, ATP-competitive, and reversible inhibitor of IKK (IC_{50} = 88 nM) with selectivity over 14 other commonly studied kinases (IC_{50} > 100 µM), including NF-κB inducing kinase. Blocks cellular IκBα phosphorylation and NF-κB activation (EC_{50} = 5 µM in TNF-α-treated HeLa cells) *in vitro* and reduces TNF-α release in plasma of LPS-challenged mice *in vivo* (50 mg/ml, p.o.).	5 mg
IKK Inhibitor XII	**401491**	A cell-permeable amino-diarylbenzamide compound that acts as a potent ATP site-targeting inhibitor against IKK-1 and IKK-2 (pIC_{50} = 6.4 and 7.0, respectively), while exhibiting more than 50-fold less potency toward a panel of greater than 50 other kinases, including IKK-3 (pIC_{50} a, IL-1ß, and IL-6 from human PBMCs (pIC_{50} = 6.1, 6.4, and 5.7, respectively) as well as TNF-α-induced NF-κB nuclear translocation in human lung fibroblast cells (pIC_{50} = 5.7).	5 mg
IKK-2 Inhibitor IV	**401481**	**{[5-(*p*-Fluorophenyl)-2-ureido]thiophene-3-carboxamide}** A cell-permeable ureidocarboxamido thiophene compound that acts as a potent, reversible, and ATP-competitive inhibitor of IKK-2 (IC_{50} = 18 nM) with selectivity over IKK-1, JNK and p38 MAPK. Inhibits TNF-α production in human monocytes (IC_{50} in the range of 0.15-2.5 µM) and blocks IL-8 and IL-6 production by synovial fibroblasts (IC_{50} = 100 nM). Further reduces paw oedema in rat arthritis model (~100% inhibition at a dose of 30 mg per kg). A 10 mM (500 µg/179 µl) solution of IKK-2 Inhibitor IV (Cat. No.401484) in DMSO is available.	500 µg
InSolution™IKK-2 Inhibitor IV	**401484**	A 10 mM (500 µg/179 µl) solution of IKK-2 Inhibitor IV (Cat. No. 401481) in DMSO.	500 µg
IKK-2 Inhibitor V	**401482**	**[N-(3,5-Bis-trifluoromethylphenyl)-5-chloro-2-hydroxybenzamide; IMD-0354]** A cell-permeable salicylamide compound that acts as an IKK-2 inhibitor by selectively blocking IκBα phosphorylation (IC_{50} ~ 250 nM) and thereby prevents the induction of NF-κB p65 nuclear translocation. Shown to offer cardioprotection by reducing IL-1ß and MCP-1 production (IC_{50} y mice by regulating adiponectin release.	5 mg
IKK-2 Inhibitor VI	**401483**	**[(5-Phenyl-2-ureido)thiophene-3-carboxamide]** An ureido-thiophenecarboxamide compound that acts as a potent, cell-permeable, reversible, and ATP-competitive inhibitor of IKK-2 (IC_{50} = 13 nM).	1 mg

NF-κB Activation Inhibitors *continued*

Product	Cat. No.	Comments	Size
IKK-2 Inhibitor VIII	**401487**	**[ACHP; 2-Amino-6-(2-(cyclopropylmethoxy)-6-hydroxyphenyl)-4-(4-piperidinyl)-3-pyridinecarbonitrile]** A cell-permeable piperidinyl-pyridine compound that acts as a selective inhibitor of IKK-2 activity (IC_{50} = 8.5 and 250 nM for IKK-2 and IKK-1, respectively) with little effect towards IKK-3, Syk, and MKK4 (IC_{50} >20 µM). Exhibits good aqueous solubility (0.12 mg/ml in pH 7.4 isotonic buffer) and potent activity in various cellular assays *in vitro* (IC_{50} *in vivo*.	1 mg
IKK-2 Inhibitor XI	**401490**	**[(5-Phenyl-3-ureido)-thiophene-2-carboxamide]** A cell-permeable thiophenecarboxamide-ureido compound that acts as a potent, ATP-binding pocket-targeting inhibitor of IKK-2 (IC_{50} = 25 nM), while affecting IKK-1 and JNK1 only at much higher concentrations (IC_{50} = 1.0 and 1.6 µM, respectively). Shown to reduce LPS-induced TNF-α production in PBMCs (IC_{50} = 250 nM) and exhibit oral availability with good pharmacokinetic in rats *in vivo*.	5 mg
IKK-2 Inhibitor, SC-514	**401479**	**(SC-514)** A cell-permeable (thienothienyl)amino-acetamide compound that displays anti-inflammatory properties. Acts as a 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). Its specificity has been confirmed using a panel of 31 other kinases, including IKK isoforms IKK-1, IKK-i, and TBK-1 (IC_{50} > 200 µM). Shown to specifically block NF-κB-dependent gene expression, but not MAP kinase pathways, in stimulated synovial fibroblasts RASF. A 25 mM (1 mg/178 µl) solution of IKK-2 Inhibitor, SC-514 (Cat. No.401485) in DMSO is also available.	1 mg
InSolution™IKK-2 Inhibitor, SC-514	**401485**	A 25 mM (1 mg/178 µl) solution of IKK-2 Inhibitor, SC-514 (Cat. No. 401479) in DMSO.	1 mg
IKK-3 Inhibitor IX	**401488**	**[5-(5,6-Dimethoxybenzimidazol-1-yl)-3-(2-methanesulfonyl-benzyloxy)-thiophene-2-carbonitrile]** A thiophenecarbonitrile compound that acts as a potent ATP-competitive inhibitor of IKK-3 (IKK-, IC_{50} = 40 nM) with ~20-fold selectivity over PLK1 and more than 125-fold selectivity over a panel of 9 other commonly studied kinases, including IKK-1/2 (IKK-α/ß). Reported to be inactive against cytochrome P450 isozymes (IC_{50} < 50 µM) 1A2, 2D6, 2C9, and 3A4.	5 mg
InhibitorSelect™ NF-κB Signaling Pathway Inhibitor Panel	**481487**	A panel containing 14 potent and selective inhibitors useful for the study of NF-κB signaling pathway. This panel contains the following inhibitors: 10 mg of BAY 11-7082 (Cat. No.196870); 1 mg of IKK Inhibitor VII (Cat. No.401486); 5 mg of Interleukin1-Receptor-Associated-Kinase-1/4 Inhibitor (Cat. No.407601); 10 mg of Histone Acetyltransferase Inhibitor II (Cat. No.382110); 5 mg of MG-132 (Cat. No.474790); 500 µg of NEMO-Binding Domain-Binding Peptide, Cell-Permeable (Cat. No.480025); 500 µg of NF-κB SN50, Cell-Permeable Inhibitor Peptide (Cat. No.481480); 5 mg of PD 98059 (Cat. No.513000); 5 mg of PDK1/Akt/Flt Dual Pathway Inhibitor (Cat. No.521275); 1 mg of Trichostatin A, *Streptomyces* sp. (Cat. No.647925); 1 mg of TIRAP Inhibitor Peptide, Cell-Permeable (Cat. No.613570), 1 mg of Tpl2 Kinase Inhibitor (Cat. No.616373), 1 mg of (5*Z*)-7-Oxozeaenol, *Curvularia* sp. (Cat. No.499610), and 5 mg of JNK Inhibitor II (Cat. No.420119). Also provided with 15 ml of anhydrous DMSO.	1 ea
Isohelenin, *Inula sp.*	**416157**	**(Isoalantolactone)** A cell-permeable sesquiterpene lactone with anti-inflammatory properties. Acts as a highly specific, potent, irreversible inhibitor of NF-κB activation that acts by preventing IκBα degradation. Does not affect the DNA binding activity of activated NF-κB, or inhibit $p59^{fyn}$ and Src kinase activities. Inhibits IL-8 gene expression in cultured human respiratory epithelium *in vitro*, and iNOS gene expression in cultured rat aortic smooth muscle cells. Offers protection against endotoxic shock *in vivo*.	1 mg
NEMO-Binding Domain Binding Peptide, Cell-Permeable	**480025**	**(DRQIKIWFQNRRMKWKKTALDWSWLQTE; NBD-Binding Peptide, Cell-Permeable)** A cell-permeable Antennapedia-NBD (wild type) fusion peptide that exhibits anti-inflammatory properties. Acts by inhibiting cytokine-induced NF-κB activation and NF-κB-dependent gene expression. Suggested to block the interaction of NEMO with the IKK (IκB)-kinase complex and thereby prevents NF-κB activation. Does not affect the TNF-α-induced phosphorylation of c-Jun and DNA binding of the transcription factor Oct-1.	500 µg
NEMO-Binding Domain Binding Peptide, Cell-Permeable, Negative Control	**480030**	**(DRQIKIWFQNRRMKWKK-TALDASALQTE; NBD-Binding Peptide, Cell-Permeable, Negative Control)** A cell-permeable Antennapedia-NBD mutated (Trp^{739} and Trp^{741} replaced with Ala) fusion peptide analog of NEMO-Binding Domain Binding Peptide (Cat. No.480025) that serves as a negative control. Shown to be defective in binding to NEMO. Does not affect the TNF-α-induced phosphorylation of c-Jun and DNA binding of the transcription factor Oct-1.	500 µg

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NF-κB Activation Inhibitors *continued*

Product	Cat. No.	Comments	Size
NF-κB Activation Inhibitor	**481406**	**[6-Amino-4-(4-phenoxyphenylethylamino)quinazoline]** A cell-permeable quinazoline compound that acts as a highly 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). Shown to exhibit anti-inflammatory effect on carrageenin-induced paw edema in rat. A 10 mM (1 mg/281 µl) solution of NF-κB Activation Inhibitor (Cat. No.481407) in DMSO is also available.	1 mg
InSolution™NF-κB Activation Inhibitor	**481407**	A 10 mM (1 mg/281 µl) solution of NF-κB Activation Inhibitor (Cat. No. 481406) in DMSO.	1 mg
NF-κB Activation Inhibitor II, JSH-23	**481408**	**(4-Methyl-N^1-(3-phenylpropyl)benzene-1,2-diamine)** A cell-permeable diamino compound that selectively blocks nuclear translocation of NF-κB p65 and its transcription activity (IC_{50} = 7.1 µM in a NF-κB reporter assay using RAW 264.7) without affecting IκB degradation. Shown to suppress DNA-binding of NF-κB and downregulate LPS-induced gene expression and apoptotic chromatin condensation.	5 mg
NF-κB Activation Inhibitor IV	**481412**	**[(E)-2-Fluoro-4′-methoxystilbene]** A cell-permeable *trans*-stilbene Resveratrol (Cat. No.554325) analog that exhibits much enhanced anti-inflammatory potency, but no anti-oxidant activity. Suppresses LPS-induced COX-2 mRNA expression in BV-2 cells (~46% inhibition at 150 nM) and Shown to be ~130-fold more potent than Resveratrol in inhibiting TNF-α-stimulated NF-κB reporter activity in 293T cells (IC_{50} = 150 nM).	10 mg
NF-κB Activation Inhibitor V	**100066**	**[5HPP-33; 5-Hydroxy-(2,6-diisopropylphenyl)-1H-isoindole-1,3-dione]** A cell-permeable N-phenylpthalimide compound that exhibits antiproliferative, antimitotic, and microtubule-stabilizing activities. Shown to exhibit potent inhibitory activity against IL-1-induced NF-κB translocation in HeLa cells (IC_{50} = 530 nM) and paclitaxel-like antimicrotubule activity. Effectively suppresses the proliferation of various cancer cells, including several Paclitaxel-resistant lines.	25 mg
NF-κB Activation Inhibitor VI	**481414**	**{BOT-64;6,6-Dimethyl-2-(phenylimino)-6,7-dihydro-5H-benzo[1,3]oxathiol-4-one}** A cell-permeable benzoxathiole compound that acts as an IKK-2 inhibitor, presumably by targeting the Ser^{177} and/or Ser^{181} residues in the kinase's activation loop domain. Shown to inhibit LPS-induced NF-κB activation and nitrite production (IC_{50} = 1.0 & 0.7 µM, respectively) in RAW 264.7 cells *in vitro* and effectively prevent LPS-induced septic death in mice (70% survival rate with 30 mg/kg BOT-64, i.p.) *in vivo*.	5 mg
NF-κB SN50, Cell-Permeable Inhibitor Peptide	**481480**	**(AAVALLPAVLLALLAPVQRKRQKLMP)** 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 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. In murine endothelial LE-II cells induced by LPS, NF-κB nuclear translocation is maximally inhibited at 18 µM.	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 Asn for Lys^{363} and Gly for Arg^{364} in the NLS region. In murine endothelial LE-II cells induced by LPS, this peptide had no measurable effect on NF-κB translocation at 18 µM.	500 µg
NF-κB Activation Inhibitor III	**481411**	**3-Chloro-4-nitro-N-(5-nitro-2-thiazolyl)-benzamide** A cell-permeable thiazoloamide compound that inhibits TNF-α-stimulated NF-κB activation and subsequent upregulation of MMP-9 in HT1080 cells (complete inhibition at 10 µM). The inhibition of MMP-9 upregulation correlates with a concomitant inhibition of TNF-α-dependent cell invasion. Does not affect TNF-α-induced AP-1 activity. The cellular target appears to be downstream of p38 activation.	5 mg
Oridonin, *R. rubescens*	**496915**	A cell-permeable diterpenoid compound that possesses anti NF-κB activity and displays antiproliferative (ED_{50} = ~ 2.7 µg/ml in lymphoid malignant cells) and antiangiogenic properties (significantly inhibits network formation of HMEC-1 cells at 2.5 µg/ml). Reported to affect DNA synthesis, induce apoptosis and initiate cell cycle arrest. Shown to efficiently block both TNF-α and LPS-induced NF-κB activity in Jurkat and in RAW264.7 murine macrophages, and inhibit p65 NF-κB transcriptional activity (IC_{50} = ~ 5 µg/ml in MT-1 cells) by disrupting NF-κB DNA-binding activity without interfering with its nuclear translocation.	5 mg
(5*Z*)-7-Oxozeaenol, *Curvularia* sp.	**499610**	**TAK1 Inhibitor** A naturally isolated cell-permeable fungal resorcylic lactone that acts as a selective and highly potent inhibitor against the MAPKKK TAK1 activity (IC_{50} = 8 nM) in an ATP-competitive and irreversible manner, while inhibiting MEK1 (IC_{50} = 411 nM) and three other MAPKKKs (IC_{50} ≥268 nM against MEKK1, ASK1, and MEKK4) only at much higher concentrations. Shown to inhibit IL-1-induced/TAK1-mediated, but not H_2O_2-induced/TAK1-independent, JNK and p38 phosphorylation in 293 cells. (5*Z*)-Zeaenol, *Curvularia* sp. (Cat. No.499609) may serve as a negative control.	1 mg

NF-κB Activation Inhibitors *continued*

Product	Cat. No.	Comments	Size
Parthenolide, *Tanacetum parthenium*	**512732**	A cell-permeable sesquiterpene lactone with anti-inflammatory, antisecretory, and spasmolytic properties. Inhibits the expression of COX-2 and proinflammatory cytokines (TNF-α and IL-1) in LPS-stimulated macrophages. Also inhibits NF-κB and activation of MAP kinase.	50 mg
PPM-18	**529570**	**(2-Benzoylamino-1,4-naphthoquinone)** 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*. Does not directly affect the enzymatic activities of iNOS or eNOS.	10 mg
Sulfasalazine	**573500**	**{5-[4-(2-Pyridylsulfamoyl)phenylazo]salicylic Acid; SSZ}** A cell-permeable anti-inflammatory agent that acts as an inhibitor of glutathione-S-transferase (IC_{50} = 10 µM in HG9 cell line). Strongly inhibits NF-κB activation and potently induces apoptosis in T-lymphocytes. Causes neutrophil apoptosis that can be abrogated by tyrosine kinase inhibitors, protein kinase A inhibitors, or antioxidants. Also inhibits basic fibroblast growth factor-induced endothelial cell chemotaxis.	100 mg
TIRAP Inhibitor Peptide, Cell-Permeable	**613570**	**[Ant-Tirap$_{138-151}$; Mal Peptide; MyD88-Adapter-Like Peptide; TIRAP Peptide; Toll-interleukin 1 Receptor (TIR) domain-containing Adapter Protein Peptide]** A cell-permeable synthetic peptide containing mouse TIRAP$_{138-151}$ fused to the *Drosophila* Antennapedia sequence. Specifically inhibits LPS-, 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**	**[Ant-Tirap$_{151-138}$; Mal Peptide; MyD88-Adapter Like Peptide; TIRAP Peptide, Control; Toll-interleukin 1 Receptor (TIR) domain-containing Adapter Protein Peptide]** A cell-permeable synthetic peptide containing mouse TIRAP$_{151-138}$, reverse sequence, fused to the *Drosophila* Antennapedia sequence. Serves as a control for TIRAP Inhibitor Peptide (Cat. No.613570).	1 mg
(5*Z*)-Zeaenol, *Curvularia* sp.	**499609**	**TAK1 Inhibitor, Inactive Control** A cell-permeable resorcylic acid lactone compound that may serve as a negative control for TAK1 (TGF-ß-Activated Kinase-1) inhibition studies. The active TAK1 inhibitor is also available, (5Z)-7-Oxozeaenol, *Curvularia* sp. (Cat. No.499610).	1 mg

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Sonic Hedgehog Signaling Inhibitors

Mammalian Hedgehog proteins include Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), and Desert Hedgehog (Dhh). Shh is expressed mainly in the epithelia in the tooth, hair, whisker, gut, bladder, urethra, vas deferens, and lung, Dhh is found in Schwann and Sertoli cell precursors and Ihh is expressed in gut and cartilage. Hedgehog proteins undergo autocatalysis to generate a ~20 kDa N-terminal domain and a ~25 kDa C-terminal domain. This autoprocessing causes the covalent attachment of cholesterol onto the carboxy-terminus of the N-terminal domain. The N-terminal domain retains all signaling capabilities while the C-terminal domain is responsible for the intramolecular precursor processing. The cholesterol moiety is believed to be responsible for directing Hedgehog traffic in the secretory cell.

Shh, a secreted morphogen, has been implicated in several embryonic developmental processes. It displays inductive, proliferative, neurotrophic, and neuroprotective properties. Shh often works in concert with the Wnt signaling protein in setting embryonic patterns. The Wnt pathway uses β-catenin to transduce its signals to the nucleus; however, the Shh pathway utilizes a 155 amino acid protein, Cubitus interruptus (Ci155) in Drosophila or Gli in mammals. In the absence of a Shh signal, Ci is targeted for proteolysis, which generates a truncated 75-amino acid residues form (Ci75) that acts as a transcriptional repressor. In vertebrates three Gli proteins (Gli1, Gli2, and Gli3) have been reported. Despite several homologous regions, including a DNA-binding domain with five C2-H2 zinc fingers and a C-terminal transcription activation domain, these proteins have distinct activities and are not considered to be functionally equivalent.

Shh signaling is known to occur through a receptor complex associating two membrane proteins, Patched (Ptc) and Smoothened (Smo). Ptc is a twelve-pass membrane protein that acts as a receptor and binds Hedgehog ligand; Smo is a seven-pass membrane protein that acts as a signal transducer. In the absence of a ligand, Ptc interacts with Smo and inhibits its activity. Shh binding to Ptc removes the inhibitory effect and allows Gli to enter the nucleus and act as a transcriptional activator. Shh signaling is required throughout embryonic development and is involved in the determination of cell fate and embryonic patterning during early vertebrate development. During the late stage of development, Shh is involved in the proper formation of a variety of tissues and organs. Shh also functions with other signaling molecules such as the fibroblast growth factors and bone morphogenetic protein to mediate developmental processes. Mutations in any of the components of the Shh pathway can lead to congenital defects and diseases, including cancer. Hence, the Shh pathway has become a potential target for drug development for the treatment of cancers and degenerative diseases.

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Sonic Hedgehog Signaling Inhibitors

Product	Cat. No.	Comments	Size
Ac-KFSTHWATYLK(-Palmitoyl)-NH_2, *all-D*	**559313**	A cell-permeable palmitoylated, retro-inverso all-D peptide spanning the second loop of integral membrane protein Smoothened (SMO) that acts as a specific and metabolically stable SMO antagonist. Shown to down-regulate the expression of Hedgehog pathway markers, namely, Gli-1, Gli-2, Gli-3, Ptch, Shh, SMO, and NES, and potently inhibit SK-Mel2 melanoma cells growth with an IC_{50} of 300 pM.	1 mg
AY 9944	**190080**	A cell-permeable amphiphilic diamine that blocks cholesterol biosynthesis and its esterification. Specifically blocks 7-dehydrocholesterol reductase (Δ^7-sterol reductase) activity with IC_{50}= 13 nM. Important tool in Sonic Hedgehog signaling and teratogenicity studies. Also reported to induce a rapid and irreversible reduction in Acidic-Sphingomyelinase activity in fibroblasts.	5 mg
Cyclopamine, *V. californicum*	**239803**	A cell-permeable steroidal alkaloid and cholesterol mimic that displays both teratogenic and antitumor activities. It disrupts cholesterol bio-synthesis and specifically antagonizes shh (Sonic Hedgehog) signaling pathway through direct interaction with Smo (smoothened), a distant relative of G-protein-coupled receptors. A valuable tool for studying the involvement of shh signaling in the development of various tumors. Tomatidine (Cat. No.614350) can be used as a negative control.	1 mg
Cyclopamine-KAAD	**239804**	**[KAAD-Cyclopamine; 3-Keto-N-(aminoethyl-aminocaproyl-dihydro- cinnamoyl)cyclopamine]** A potent, cell-permeable analog of Cyclopamine (Cat. No.239803) that specifically inhibits the Hedgehog (Hh) signaling with similar or lower toxicity (IC_{50} = 20 nM in Shh-LIGHT2 assay; 50 nM in $p2^{Ptch-/-}$cells; 500 nM in SmoA1-LIGHT cells). Binds to SmoA1 and promotes its exit from the endoplasmic reticulum. Suppresses both the ShhNp-induced pathway activity and SmoA1-induced reporter activity.	100 µg

Sonic Hedgehog Signaling Inhibitors *continued*

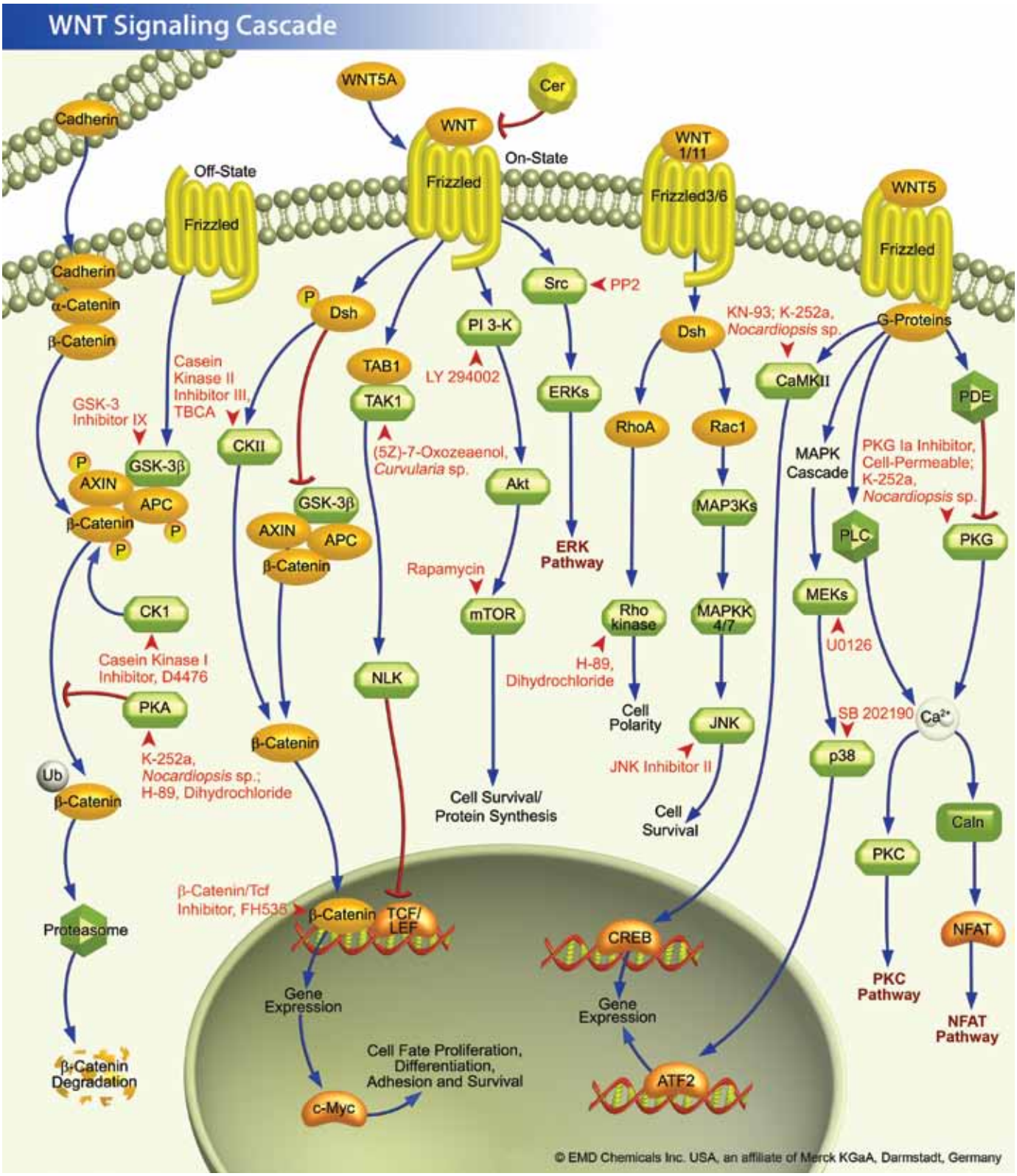
Product	Cat. No.	Comments	Size
Hedgehog Antagonist VIII	**373402**	**1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-((3-(4-fluorophenyl)-3,4-dihydro-4-oxo-2-quinazolinyl)methyl)-urea** A cell-permeable quinazolinyl-urea compound that is shown to potently inhibit OCT-Shh-stimulated Gli transcription activity in a 10t1/2(s12) cell-based Luciferase reporter assay (IC_{50} = 70 nM).	5 mg
Hh Signaling Antagonist VII	**373385**	**{JK184; N-(4-Ethoxyphenyl)-4-(2-methylimidazo[1,2-a]pyridin-3-yl)thiazol-2-amine}** A cell-permeable imidazopyridine compound that acts as downstream Hedgehog (Hh) pathway blocker by directly targeting the enzymatic activity of Adh7 (IC_{50} = 210 nM), the class IV alcohol dehydrogenase. Inhibits Hg-Ag-induced Gli-transcription activity (IC_{50} = 30 nM) as well as Gli1 and Ptc1 mRNA expression in a dose-dependent manner in H3H10T1/2 cells. Shown to exhibit ≥100-fold greater cytotoxicity towards five Hh activated tumor cells (GI_{50} ≤21 nM vs. 1.6 µM for the non-Hh activated H3H10T1/2 cells) *in vitro* and inhibit the growth of two xenografted tumors in mice (30-50% inhibition, 0.2 mg/mouse/day by p.o.) *in vivo*. Also acts as a microtubule-depolymerizing agent.	5 mg
Hh/Gli Antagonist	**373400**	**{GANT58; NSC 75503; 4-(2,4,5-Tri(pyridin-4-yl)thiophen-3-yl)pyridine}** A cell-permeable tetrapyridinylthiophene compound that acts as downstream Hedgehog (Hh) pathway blocker and targets Gli-mediated gene transactivation (IC_{50} ~ 5 µM in SAG-stimulated Shh-L2 cells). Its action appears to be Hh pathway-selective, downstream of Smo and Sufu, but does not seem to interfere with Gli DNA binding. Shown to reduce cellular mRNA levels of Hh target genes, *Gli1*, *Hip1*,& *Ptch*, and inhibit Gli-dependent tumor growth both *in vitro* and *in vivo*.	5 mg
Hh/Gli Antagonist	**373401**	**[GANT61; NSC 136476; 2-((3-(2-(Dimethylamino)benzyl)-2-(4-pyridinyl)tetrahydro-1(2H)-pyrimidinyl)methyl)-N,N-dimethylaniline]** A cell-permeable hexahydropyrimidine compound that displays similar pharmacological property as, but is structurally disctinct from, GANT58 (Cat. No.373400). While both compounds act as downstream Hedgehog (Hh) pathway-selective blockers and target Gli-mediated gene transactivation with similar potency (IC_{50} = ~ 5 µM) in SAG-stimulated Shh-L2 cells, GANT61 does exhibit better *in vivo* antitumor efficacy, presumably due to its superior pharmacokinetics, and only GANT61, but not GANT58, is shown to inhibit Gli DNA binding in HEK293 cells.	5 mg
Jervine	**420210**	**[(3ß, 23ß)-17,23-Epoxy-3-hydroxyveratraman-11-one; 11-Ketocyclopamine]** A cell-permeable steroidal alkaloid similar to cyclopamine (Cat. No.239803) that displays teratogenic effects and induces cyclopia by blocking shh (Sonic Hedgehog) signaling (IC_{50} = ~ 500-700 nM in s12 cells). Tomatidine (Cat. No.614350) serves as a suitable negative control.	1 mg
SANT-1	**559303**	A potent, cell-permeable antagonist of the Shh (Sonic Hedgehog) signaling pathway (IC_{50} = 20 nM in the Shh-LIGHT2 assay and in $Ptch1^{-/-}$ cells) by binding directly to Smoothened (Smo; K_d = 1.2 nM), a distant relative of G protein-coupled receptors. 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
Smoothened Agonist	**566660**	**{$SAG_{1.3}$; N-Methyl-N'-(3-pyridinylbenzyl)-N'-(3-chlorobenzo[b]thiophene-2-carbonyl)-1,4-diaminocyclohexane}** A cell-permeable benzothiophene compound that modulates the coupling of Smo with its downstream effector by interacting with the Smo heptahelical domain (K_D = 59 nM). Shown to induce Hedgehog pathway activation (EC_{50} = ı 3 nM in NIH 3T3-derived Shh-LIGHT2 cells) and counteracts Cyclopamine-KAAD (Cat. No.239804) inhibition of Smo. Reported to act as an activator at low concentrations and as an inhibitor at very high concentrations. A 10 mM (500 µg/86 µl) solution of Smoothened Agonist, SAG (Cat. No.566661) in H_2O is also available.	1 mg
Tomatidine, HCl	**614350**	A steroidal alkaloid that structurally resembles Cyclopamine (Cat. No.239803), but lacks the capacity to inhibit Shh (Sonic Hedgehog) signaling. Reported to be non-teratogenic.	25 mg
U18666A	**662015**	**[3ß-(2-Diethylaminoethoxy)androst-5-en-17-one, HCl]** 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 Δ^8-sterol isomerase.	10 mg
Veratramine, HCl, **V. californicum**	**676925**	**[14,15,16,17-Tetrahydroveratraman-3ß,23ß-diol, HCl]** A cell-permeable steroidal alkaloid that is structurally related to and serves as a suitable inactive control for Cyclopamine (Cat. No.239803), Cyclopamine-KAAD (Cat. No.239804), and Jervine (Cat. No.420210) in Shh (sonic hedgehog) signaling studies.	5 mg

Stem Cell Proliferation Inhibitors

Product	Cat. No.	Comments	Size
Stem Cell Proliferation Inhibitor	**569620**	**(Ac-SDKP; Goralatide; Seraspenide)** A tetrapeptide that acts as a natural inhibitor of pluripotent hematopoietic stem cell proliferation. Protects bone marrow against chemotherapeutic agents, ionizing radiations, hyperthermy, or phototherapy-induced toxicity. Inhibits cardiac fibroblast proliferation, collagen synthesis, and activation of p42/p44 MAP kinases. Cleaved to an inactive form by angiotensin I-converting enzyme (ACE).	5 mg

NEW! StemSelect™ Small Molecule Regulators 384-Well Library I (Cat. No. 569744) - See page 55 for details.

Highlighted below are inhibitors included in InhibitorSelect™ Wnt Signaling Pathway Inhibitor Panel (Cat. No. 681666). See page 205 for details.



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Wnt Signaling Inhibitors

Product	Cat. No.	Comments	Size
ß-Catenin/Tcf Inhibitor, FH535	**219330**	**[N-(2-Methyl-4-nitro)-2,4-dichlorosulfonamide]** A cell-permeable sulfonamide compound that acts as a dual pathway inhibitor against Wnt/ß-catenin (≥80% inhibition at 15 µM in ß-catenin/Tcf-dependent cellular reporter assays) and PPARγ/δ (≥30% inhibition at 0.5 µM in PPRE cellular reporter assays) signalings. Although both FH535 and the structurally similar PPARγ-selective inhibitor GW9662 (Cat. No.370700) inhibit coactivator/PPAR binding, only FH535 blocks ß-catenin/PPARγ interaction and the antagonistic activity of FH535 does not involve the covalent modification of or non-covalent interaction with the PPAR ligand-binding site cystein residue that is crucial for GW9662 action.	10 mg
GW9662	**370700**	**2-Chloro-5-nitro-N-phenylbenzamide** A cell-permeable, selective and irreversible PPARγ antagonist (IC_{50} = 3.3 nM, 32 nM, and 2 µM for PPARγ, PPARα, and PPARδ, respectively). Reported to covalently modify a cysteine residue in the binding site of PPAR. At a concentration of 10 µM, also acts as an agonist of human pregnane X receptor (PXR) and farnesoid X receptor (FXR). Does not activate liver X receptor-α ($LXR_α$), retinoic acid receptor (RAR), retinoid X receptor-α ($RXR_α$) and thyroid receptors α and ß ($TR_α$ and $TR_ß$).	5 mg
IQ-1	**412400**	**[2-(4-Acetylphenylazo)-2-(3,3-dimethyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetamide]** A cell-permeable tetrahydroisoquinolinylidene compound that modulates Wnt/ß-catenin signaling by targeting the PR72/130 subunit of PP2A and thereby blocking PP2A/Nkd complex formation, resulting in diminished ß-catenin/p300 interaction and a concomitant increase in ß-catenin/CBP usage. Co-administration of IQ-1 (4 µg/ml) and Wnt3a (100 ng/ml), but neither reagent alone, has been shown to be sufficient in maintaining long-term (>48 days) murine ESCs (Embryonic Stem Cells) pluripotency in the absence of serum.	10 mg
Wnt Antagonist I, IWR-1-*endo*	**681669**	**Wnt Pathway Inhibitor I** A cell-permeable *p*-imidobenzamidoquinoline, *endo*-diastereomer that is shown to inhibit the activity of TNKS1/PARP5a and TNKS2/PARP5b in *in vitro* auto-PARsylation assays (IC_{50} = 131 and 56 nM, respectively) and effectively suppress Wnt-stimulated transcription activity in L-Wnt-STF-based reporter assays (IC_{50} = 180 nM), while exhibiting little activity against PARP1 or PARP2 (IC_{50} >18.75 µM). Although both IWR-1-*endo* and XAV939 act as reversible Wnt pathway inhibitors and exhibit similar pharmacological effects both *in vitro* and *in vivo*, IWR-1-*endo* exerts its effect via interaction with Axin, while XAV939 binds TNKS directly.	10 mg
Wnt Antagonist II, IWP-2	**681671**	**(Inhibitor of Wnt Production-2)** A cell-permeable benzothiazolyl-acetamide compound that inhibits the cellular Wnt processing and secretion via selective blockage of MBOAT (membrane-bound O-acyltranferase) family member Porcn- (Porcupine) mediated Wnt palmitoylation. IWP-2 does not affect Wnt/ß-catenin signaling pathway in general and, unlike IWR-1-*endo* (Cat. No.681669), displays no effect against Wnt-stimulated cellular responses.	10 mg
Wnt Synergist, QS11	**681668**	**Wnt Pathway Activator II** A cell-permeable purine compound that binds ARFGAPs (K_d = 364 and 620 nM for AMAP1 and ARFGAP1, respectively) and acts as a broad specificity ARFGAPs inhibitor (GTPase activating proteins of ADP-ribosylation factor). Shown to synergize with Wnt-3a and specifically activate the canonical Wnt/ß-catenin signaling pathway both *in vitro* (2-, 40-, and 200-fold increase of basal transcription activity by QS11, Wnt-3a, and QS11/Wnt-3a, respectively, in a Super(8X)TOPFlash reporter assay using HEK293 cells) and *in vivo* (in the induction of *Xenopus* embryonic axis duplication). Also reported to block the migration of AMAP1-overexpressing MDA-MB-231 cells (86% inhibition at 2.5 µM).	5 mg

Angiogenesis Inhibitors

Product	Cat. No.	Comments	Size
Fumagillin, *Aspergillus fumigatus*	**344845**	**Fumidil B** Antiprotozoal agent and angiogenesis inhibitor. Acts as an inhibitor of methionine amino-peptidase 2.	500 µg
4-Hydroxyphenylretinamide	**390900**	**Fenretinide, 4HPR, N-(4-Hydroxyphenyl)-all-*trans* Retinamide** A synthetic amide of all-*trans* retinoic acid (RA) that displays reduced toxicity relative to RA while maintaining significant biological activity. Active in the prevention and treatment of a variety of neoplasms in animals. Inhibits human breast cancer, prostate adenocarcinoma, and ovarian carcinoma cell proliferation. Inhibits angiogenesis as well as endothelial cell motility and tubule formation. Induces apoptosis in malignant hemopoietic cell lines.	5 mg
2-Methoxyestradiol	**454180**	**2-Methoxy-3,17b-dihydroxyestra-1,3,5(10)-triene** A natural metabolite of 17ß-estradiol that is devoid of estrogenic activity. Inhibits cell proliferation and angiogenesis. Markedly inhibits the neovascularization of solid tumors and suppresses tumor growth in mice. Binds to the colchicine binding site of tubulin, and has been suggested to function as a natural regulator of microtubule assembly and function.	10 mg 50 mg
(±)-Thalidomide	**585970**	**(±)-2-(2,6-Dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione** Selective inhibitor of TNF-α biosynthesis. Blocks basic fibroblast growth factor (bFGF)-induced angiogenesis in cornea. An immunomodulator that inhibits replication of the HIV-1 virus. Has been used to treat AIDS-related oral ulcers.	100 mg
Tranilast	**616400**	**N-(3',4'-Dimethoxycinnamoyl)anthranilic Acid** An anthranilic acid analog that acts as a potent inhibitor of VEGF- and vascular permeability factor-induced angiogenesis and collagen synthesis. Inhibits VEGF- and PMA-stimulated PKC activity in retinal capillary endothelial cells without affecting the VEGF binding or VEGF receptor phosphorylation. Also has antiallergic, anti-inflammatory, and antiproliferative properties. Induces Ca^{2+} mobilization in vascular smooth muscle.	10 mg
Withaferin A, *Withania somnifera*	**681535**	A cell-permeable steroidal lactone that displays antitumor, anti-inflammatory, radiosensitizing, and immunosuppressive properties. Potently inhibits angiogenesis both *in vitro* (IC_{50} = 12 nM against HUVEC proliferation) and *in vivo* (80% inhibition at 7 µg/kg/day in C57BL/6J mice, s.c.) and NF-κB activation (IC_{50} = 500 nM in TNF-α-induced endothelial cells) by targeting the ubiquitin-mediated proteasome pathway. At higher concentrations (~5 µM) also affects AP-1 transcription and induces cell death.	5 mg

Cell Proliferation and Sheet Migration Inhibitors

Product	Cat. No.	Comments	Size
TAS-301	**608050**	**3-bis(4-Methoxyphenyl)methylene-2-indolinone** A cell-permeable indolinone compound that displays anti-proliferative properties. Potently inhibits growth factor-induced VSMCs (vascular smooth muscle cells) migration and proliferation by blocking voltage-independent Ca^{2+} influx and downstream signals such as Ca^{2+}/PKC-signaling pathway, leading to AP-1 induction and inhibition of cytoskeletal depolymerization. Reported to prevent neointimal thickening following balloon injury to rat carotid and porcine coronary arteries.	10 mg 25 mg

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Adenosine Kinase Inhibitors

Product	Cat. No.	Comments	Size
Adenosine Kinase Inhibitor	**116890**	**{ABT-702; 4-Amino-5-(3-bromophenyl)-7-(6-morpholino-pyridin-3-yl)pyrido[2,3-d]pyrimidine, 2HCl}** A cell-permeable, non-nucleoside pyridopyrimidine compound that acts as a potent, adenosine-competitive, and reversible adenosine kinase (AK) inhibitor (IC_{50} = 50.7 nM using intact IMR-32 cells and 1.7 nM in cell-free assays using rat brain cytosolic AK). The inhibitory effect is not species-specific and its pharmacological selectivity is confirmed using a panel of more than 80 other enzymes, ion channels, and receptors, including various adesine receptors. It readily crosses the blood-brain barrier and is shown to be efficacious in *in vivo* animal models via various administration methods (i.p., p.o., s.c.).	5 mg

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.

At least nine different isoforms of AC have been reported that differ in their regulatory properties and are differentially expressed in various tissues. They are integral membrane proteins that are 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 activates CaM-dependent phosphodiesterase.

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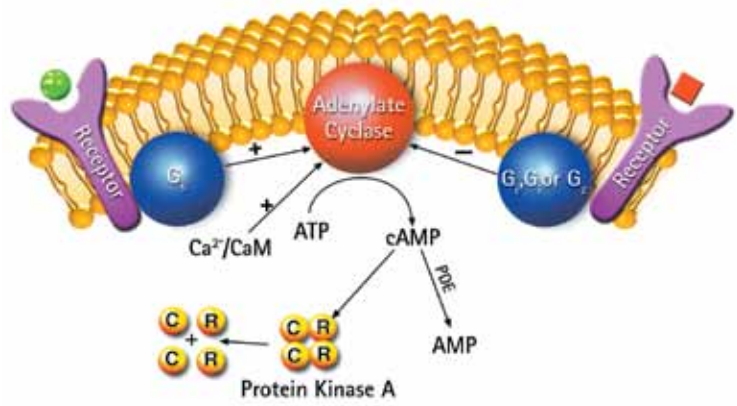

Adenylate Cyclase Inhibitors

Product	Cat. No.	Comments	Size
Adenylyl Cyclase Type V Inhibitor, NKY80	**116850**	**[2-Amino-7-(furanyl)-7,8-dihydro-5(6H)-quinazolinone]** A cell-permeable quinazolinone containing a non-nucleoside compound that acts as a potent, selective inhibitor of adenylyl cyclase (AC) type V isoform (IC_{50} = 8.3 µM, 132 µM and 1.7 mM for type V, III and II, respectively) in the presence of $G_s\alpha$ GTPγS-Forskolin. Displays ~210-fold greater selectivity for type V over the type II isoform. The inhibition is non-competitive with respect to ATP and Forskolin. Regulates the AC catalytic activity in heart and lung tissues.	5 mg 25 mg
Angiotensin II, Human	**5230101**	**(DRVYIHPF)** Plays an important role in the regulation of blood pressure. Stimulates the release of aldosterone from the adrenal gland. Inhibits adenylate cyclase activity in spontaneously hypertensive rats. Has strong vasoconstrictive effects. Increases the entry of Ca^{2+} in heart muscle via voltage-sensitive channels and activates myosin light chain kinase. Also elicits an increase in voltage-dependent delayed rectifier K^+ current in neurons. Activates JAK2 in smooth muscle cells. Activates $p125^{FAK}$ and a cytosolic 115-120 kDa calcium-dependent tyrosine kinase in rat epithelial cells. Also activates $p60^{c\text{-}src}$ as well as ERK1/2, JNK, and p38 MAP Kinase in vascular smooth muscle cells.	1 mg 5 mg 25 mg
2',5'-Dideoxyadenosine	**288104**	**(2',5'-dd-Ado)** Cell-permeable, non-competitive adenylate cyclase inhibitor (IC_{50} = 3 µM), that binds to the adenosine P1 binding site. Blocks positive inotropic and chronotropic effects of ß-adrenergic agents.	1 mg
InSolution™MANT-GppNHp	**444168**	**{mant-GMPPNP; 2'/3'-O-(N-Methylanthraniloyl)-guanosine-5'-[(ß,γ)-imido] triphosphate, Triethylammonium Salt; 2'/3'-O-(N-Methylanthraniloyl)-ß,γ-imidoguanosine-5'-triphosphate, Triethylammonium Salt}** A more lipophilic, fluorescent derivative of the GTP-hydrolysis-resistant GTP analog, GppNHp. Useful for investigating the interactions of low molecular weight GTP-binding proteins with their specific effector proteins. Acts as a potent, competitive inhibitor of adenylyl cyclase (AC; K_i = 161 nM and 155 nM in forskolin/Mn^{2+}-stimulated AC in S49 *cyc*$^-$ membranes and insect cell membranes, respectively). Shown to bind to G_o-proteins with high affinity, $G_s\alpha$-$G_i\alpha$-proteins with low affinity, and ineffective at activating Gα.	50 µl
MDL-12,330A, Hydrochloride	**444200**	**[*cis*-N-(2-Phenylcyclopentyl)azacyclotridec-1-en-2-amine, HCl]** Cell-permeable and irreversible inhibitor of adenylate cyclase (IC_{50} = 250 µM).	1 mg
Melittin	**444605**	A 26-residue polypeptide from bee venom that binds calmodulin in a Ca^{2+}-dependent manner. A stimulator of $G_i\alpha$ and $G_{11}\alpha$ activity that is reported to inhibit adenylate cyclase activity in synaptic membranes. Activates phospholipase A_2 and inhibits protein kinase C (IC_{50} = 5-7 µM) by binding to the catalytic domain in a Mg^{2+}-ATP sensitive manner. Has also been used for affinity purification of several Ca^{2+}-binding proteins.	250 µg
SQ 22536	**568500**	**[9-(Tetrahydro-2'-furyl)adenine]** Cell-permeable adenylate cyclase inhibitor. Blocks PTH-stimulation of adenylate cyclase (IC_{50} = 200 µM). Reduces PGE_2-induced inhibition of $O_2^{\cdot-}$ production.	5 mg

ß Adrenergic Receptor Kinase Inhibitors

Product	Cat. No.	Comments	Size
ßARK1 Inhibitor	**182200**	**ß-Adrenergic Receptor Kinase1 Inhibitor** A selective inhibitor of ßARK1 (ß-Adrenergic Receptor Kinase 1) (IC_{50} = 126 µM). Has no inhibitory activity against protein kinase A (PKA).	5 mg

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Angiotensin-Converting Enzyme (ACE) Inhibitors

The renin-angiotensin system plays an important role in electrolyte balance and fluid regulation. 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**	**([2S]-1-[3-Mercapto-2-methylpropionyl]-L-proline; SQ-14225)** An antihypertensive agent that competitively inhibits angiotensin-converting enzyme (ACE; IC_{50}= 23-35 nM) and acts as a reversible and competitive inhibitor of LTA_4 hydrolase (IC_{50} = 11 µM). Inhibits angiogenesis and slows the growth of experimental tumors in rats. Reported to inhibit apoptosis in human lung epithelial cells (IC_{50} = ~ 320 nM).	1 g
DL-Thiorphan	**598510**	**N-[(RS)-2-Benzyl-3-mercaptopropanoyl]-glycine** A thiol containing amido-acid that selectively binds to the active site zinc of metalloproteinases and blocks their activity (IC_{50} = 2.1 nM for neutral endopeptidase-NEP). Although it is shown to inhibit the activity for Aß peptide degrading enzyme neprilysin *in vitro*, it has no effect on the secretion of Aß peptide or amyloid ß precursor protein (APP). Also reported to inhibit the activity of angiotensin-converting enzyme (ACE) at much higher concentrations (IC_{50} = 14 µM); however, it does not affect the activity of endothelin-converting enzyme.	10 mg
TAPI-2	**579052**	**{N-(R)-[2-(Hydroxyaminocarbonyl)methyl]-4-methylpentanoyl-L-*t*-butyl-alanyl-L-alanine, 2-aminoethyl Amide; TNF-α Protease Inhibitor-2}** A hydroxamate-based inhibitor of MMPs and TACE. Inhibits the activation-induced shedding of L-selectin from neutrophils, eosinophils, and lymphocytes, as well as phenylarsine oxide (PAO)-induced shedding in neutrophils. Also acts as a weak inhibitor of angiotensin converting enzyme (IC_{50} = 18 µM).	1 mg

Aromatase Inhibitors

Product	Cat. No.	Comments	Size
Aromatase Inhibitor I	**182540**	A potent, competitive, nonsteroidal inhibitor of aromatase (P450arom; IC_{50} = 40 nM for human aromatase). Reported to be more potent than fadrozole in inhibiting aromatase activity. Does not significantly inhibit 17α-hydroxylase.	1 mg

Autophagy Inhibitors

Product	Cat. No.	Comments	Size
Autophagy Inhibitor	**189490**	**(3-MA; 3-Methyladenine)** A widely used cell-permeable autophagic sequestration blocker that effectly protects cerebellar granule cells from apoptosis following serum/potassium deprivation. Although a known class III PI3K inhibitor (IC_{50} = 4.5 mM in cell-free enzymatic assays), 3-MA exhibits quite distinct pharmacological properties from those of two other PI3K inhibitors, LY 294002 (Cat. Nos.440202 and440204) and Wortmannin (Cat. No.681675)	50 mg

Catalase Inhibitors

Product	Cat. No.	Comments	Size
3-Amino-1,2,4-triazole	**165421**	**3-Amino-1,2,4-triazole** An irreversible inhibitor of catalase. Useful in studying free radical-induced tissue injury. Inhibits rat brain catalase *in vivo*. Also useful for the determination of tryptophan in proteins.	1 g

CFTR Inhibitors

Product	Cat. No.	Comments	Size
CFTR Inhibitor II, GlyH-101	**219671**	**[N-(2-Naphthalenyl)-((3,5-dibromo-2,4-dihydroxyphenyl) methylene)glycine hydrazide]** A cell-permeable glycinyl hydrazone compound that acts as a potent, selective and reversible open-channel blocker of CFTR with intermediate speed (i = 4.3 µM in CFTR-expressing FRT cells for apical membrane Cl^- current) and exhibits desirable aqueous solubility. Shown to produce inwardly rectifying CFTR Cl^- currents with reduced mean channel open time and suggested to directly interact with the channel pore at the extracellular side of the membrane. Displays minimal effects on P-glycoprotein and non-CFTR-mediated Cl^- currents, and is effective in nasal and intestinal epithelia *in vivo*.	5 mg
CFTR-F508del Corrector, KM11060	**219676**	**7-Chloro-4-(4-((4-chlorophenyl)sulfonyl)piperazino)quinoline** A cell-permeable sulfonylpiperazine compound that is shown to boost the surface expression of cellular F508del-CFTR in a time- and dose-dependent manner and help restore CFTR function in F508del-CFTR-expressing cells (Effective concentration 10 µM). Evidence indicates that a correction of trafficking at the level of ER coupled with a transient increase of cellular cGMP due to PDEV (Cat. Nos.524715 and524738) inhibition as part of the cellular mechanism that accounts for the observed pharmacological effects of KM11060.	5 mg

DAO Inhibitors

Product	Cat. No.	Comments	Size
D-Amino Acid Oxidase Inhibitor	**138000**	**{D-AAO Inhibitor; Compound 8; 4H-Thieno[3,2-b]pyrrole-5-carboxylic acid}** A cell-permeable thienopyrrole compound that potently inhibits the cellular activity of transfected D-amino acid oxidase (DAO/DAAO/DAM0X/0XDA) in CHO cells (IC_{50} against human and rat DAO = 145 and 114 nM, respectively), while exhibiting no activity towards D-aspartate oxidase (DDO; IC_{50} >5 µM), P450 enzymes CYP3A4/2D6/3C9 (IC_{50} >10 µM), and a panel of over 150 other enzymes, receptors, and ion channels. Although *in vivo* treatment of Compound 8 (200 mg/kg, i.p.) is shown to effectively inhibit DAO activity in rat brain and kidney (by 96% and 80%, respectively), the resulting D-serine concentration increase in the periphery and central nervous system appears to be far from sufficient to produce adequate antipsychotic and cognitive enhancing effects.	50 mg

Epoxide Hydrolase Inhibitors

Product	Cat. No.	Comments	Size
Soluble Epoxide Hydrolase Inhibitor, NCND	**324813**	**1-Cyclohexyl-3'-dodecylurea, N-Cyclohexyl-N'-dodecylurea** A cell-permeable 1,3-disubstituted urea compound that displays anti-hypertensive and anti-inflammatory properties. Acts as a potent, selective, competitive, and tight-binding transition-state analog inhibitor of soluble epoxide hydrolase (sEH; IC_{50} = 9.8 nM for mouse recombinant sEH, 85.2 nM for human recombinant sEH). Reported to decrease human VSMC (vascular smooth muscle cell) proliferation.	25 mg

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

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 anticancer agents. Since Ras proteins are posttranslationally 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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Farnesyltrasferase (FTase), Geranylgeranyltransferase (GGTase), and Methyltransferase Inhibitors

Product	Cat. No.	Comments	Size
5′-Deoxy-5′-methylthioadenosine	**260585**	**(MeSAdo; MTA)** A cell-permeable, reversible, and ATP-competitive naturally-occurring co-product of polyamine biosynthesis that acts as an endogenous substrate of methylthioadenosine phosphorylase (MTAP). Potently inhibits the protein carboxymethyltransferase and induces apoptosis in leukemia U937 cells. Also inhibits FGF-2 receptor tyrosine kinase activity as well as the proliferation of human astrocytes and glioma cells.	50 mg
FPT Inhibitor I	**344150**	**{(E,E)-2-[(Dihydroxyphosphinyl)methyl]-3-oxo-3-[(3,7,11-trimethyl-2,6,10-dodecatrienyl)-amino]propanoic Acid, 3Na}** Potent and highly selective inhibitor of farnesyltransferase (FTase; IC_{50} = 83 nM). Inhibits geranylgeranyltransferase (GGTase) I and II at much higher concentrations (IC_{50} = 26 µM and 47 µM for GGTase I and II, respectively).	1 mg
FPT Inhibitor II	**344152**	**{(E,E)-2-[2-Oxo-2-[[(3,7,11-trimethyl-2,6,10-dodecatrienyl) oxy] amino]ethyl]phosphonic Acid, 2Na}** A cell permeable potent and selective inhibitor of farnesyltransferase (FTase; IC_{50} = 75 nM). Also inhibits Ras farnesylation in whole cells by ~90% at 25-250 µM. Resistant to cleavage by phosphorylation.	1 mg
FPT Inhibitor III	**344154**	**{(E,E)-[2-Oxo-2-[[(3,7,11-trimethyl-2,6,10-dodecatrienyl)oxy]amino] ethyl] phosphonic Acid, (2,2-Dimethyl-1-oxopropoxy)methyl Ester, Na}** A cell-permeable prodrug ester form of farnesyltransferase (FTase) inhibitor II (Cat. No.344152). Also inhibits Ras processing in cells (~100 µM), thereby preventing Ras-mediated transformation. Inhibits C15 and C20 protein prenylation in NIH-3T3 cells.	1 mg
FTase Inhibitor I	**344510**	**{N-[2(S)-[2(R)-Amino-3-mercaptopropylamino]-3-methylbutyl]-Phe-Met-OH; B581}** A potent, cell-permeable, selective, peptidomimetic inhibitor of farnesyltransferase (FTase) that is approximately 37-fold more active against FTase (IC_{50} = 21 nM *in vitro*) than against geranylgeranyltransferase (GGTase; IC_{50} = 790 nM). Very resistant to proteolysis.	1 mg
FTase Inhibitor II	**344512**	**(H-Cys-4-Abz-Met-OH)** Potent farnesyltransferase (FTase) inhibitor (IC_{50} = 50 nM). Prevents the farnesylation of Ras, resulting in its inability to associate with other cell signaling components in the cell.	1 mg
FTase Inhibitor III	**344514**	**[H-Cys-Val-2-Nal-Met-OH(Nal= 2-naphthylalanine)]** A potent synthetic inhibitor of $p21^{ras}$ farnesyltransferase (FTase; IC_{50} = 12 nM).	1 mg

Farnesyltrasferase (FTase), Geranylgeranyltransferase (GGTase), and Methyltransferase Inhibitors *continued*

Product	Cat. No.	Comments	Size
FTI-2148	**344557**	**[2-(((5-((1H-Imidazol-4-ylmethyl)-amino)-methyl)-2'-methyl-biphenyl-2-carbonyl)-amino)-4-methylsulfanyl-butyric acid, 2TFA]** An imidazolo-containing peptidomimetic that preferentially inhibits protein farnesyltransferase activity (IC_{50} = 820 pM for mammalian, 1.8 nM for *T. brucei* and 15 nM for *P. falciparum*) compared to protein geranylgeranyltransferase-I (IC_{50} > 1.7 µM for mammalian). Shown to disrupt Ras farnesylation in H-Ras-transformed NIH3T3 cells (IC_{50} = 60 nM) and prevent the growth of *T. brucei rhodesiense* and *T. brucei brucei* (ED_{50} = 200 nM and 1 µM, respectively).	500 µg
FTI-2628	**344559**	**[2-(((5-((1H-Imidazol-4-ylmethyl)-amino)-methyl)-2'-methyl-biphenyl-2-carbonyl)-amino)-4-methylsulfanyl-butyric acid benzyl ester]** A cell-permeable benzyl ester prodrug form of FTI-2148 (Cat. No.344557) that preferentially inhibits protein farnesyltransferase activity (IC_{50} = 530 nM for mammalian and 1.0 µM for *P. falciparum*) over protein geranylgeranyltransferase-I (IC_{50} > 10 µM for mammalian) and displays anti-malarial properties. Potently disrupts Ras farnesylation in H-Ras-transformed NIH 3T3 cells (IC_{50} = 20 nM) and inhibits the growth of *P. falciparum* in red blood cells (ED_{50} = 150 nM). Also suppresses parasitemia in *P. berghei*-infected mice by 46.1% (50 mg/kg, ip) with no apparent toxicity.	500 µg
FTI-276	**344550**	**{N-[2-phenyl-4-N[2(R)-amino-3-mercaptopropylamino benzoyl]-methionine, TFA}** A highly potent and selective CAAX peptidomimetic of the carboxyl terminal of Ras proteins that inhibits farnesyl transferase (FTase) *in vitro* (IC_{50} = 500 pM). Inhibits geranylgeranyltransferase I (GGTase I) at much higher concentration (IC_{50} = 50 nM). Has been shown to selectively block the growth of a human lung carcinoma expressing oncogenic K-Ras in nude mice. Also inhibits oncogenic signaling and tumor growth of NIH 3T3 cells transformed with the Ras oncogene at 20 µM.	250 µg
FTI-277	**344555**	**{Methyl {N - [2-phenyl-4-N [2(R)-amino-3-mecaptopropylamino] benzoyl]}-methionate, TFA}** Prodrug form of FTI-276 (Cat. No.344550) that acts as a highly potent and selective inhibitor of FTase (IC_{50} = 50 nM). Inhibits H-Ras processing in whole cells (IC_{50} = 100 nM), but it does not inhibit geranylgeranylated Rap1A processing even at 10 µM. Induces accumulation of non-farnesylated cytoplasmic H-Ras, which binds to Raf protein to form inactive Ras/Raf complexes. FTI-277 is also highly effective and selective in disrupting constitutive H-Ras-specific activation of MAP kinase. Induces apoptosis in v-K-*ras*-transformed normal rat kidney (KNRK) cells, but not in control NRK cells.	250 µg
GGTI-2133	**345884**	**{4-[[N-(Imidazol-4-yl)methyleneamino]-2-(1-naphthyl)benzoyl]leucine}** A cell-permeable non-thiol peptidomimetic that acts as a potent and selective inhibitor of geranylgeranyltransferase I (GGTase I; IC_{50} = 38 nM) with a 140-fold selectivity over farnesyltransferase (FTase; IC_{50} = 5.4 µM).	250 µg
GGTI-2147	**345885**	**{4-[[N-(Imidazol-4-yl)methyleneamino]-2-(1-naphthyl)benzoyl]leucine methyl ester}** A cell-permeable non-thiol peptidomimetic that acts as a potent and selective inhibitor of geranylgeranyltransferase I (GGTase I). Blocks the geranyl-geranylation of Rap1A with an IC_{50} value that is 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
GGTI-286	**345878**	**{N-4-[2(R)-Amino-3-mercaptopropyl]amino-2-phenylbenzoyl-(L)-leucine methyl ester, TFA}** A potent, cell-permeable, and selective inhibitor of GGTase I. This methyl ester derivative of GGTI-287 (Cat. No.345880) is about 25-fold more potent (IC_{50} = 2 µM vs. 50 µM) than FTI-277 (Cat. No.344555) in inhibiting the processing of the geranylgeranylated protein Rap1A. Selectively antagonizes oncogenic K-Ras4B (IC_{50} = 2 µM). GGTI-286 has also been shown to have a significant antiproliferative effect in human malignant glioma cells.	250 µg
GGTI-287	**345880**	**{N-4-[2(R)-Amino-3-mercaptopropyl]amino-2-phenylbenzoyl-(L)-leucine,TFA}** A highly potent and selective peptidomimetic inhibitor of geranylgeranyltransferase I (GGTase I) relative to farnesyltransferase (FTase) *in vitro* (IC_{50} = 5 nM and 25 nM, respectively).	250 µg
GGTI-297	**345882**	**{N-4-[2(R)-Amino-3-mercaptopropyl]amino-2-naphthylbenzoyl-(L)-leucine, TFA}** A potent, cell-permeable, and selective peptidomimetic inhibitor of geranylgeranyltransferase I (GGTase I; IC_{50} = 50 nM) relative to farnesyltransferase (FTase; IC_{50} = 200 nM).	250 µg

Farnesyltrasferase (FTase), Geranylgeranyltransferase (GGTase), and Methyltransferase Inhibitors *continued*

Product	Cat. No.	Comments	Size
GGTI-298	**345883**	**{N-4-[2(R)-Amino-3-mercaptopropyl]amino-2-naphthylbenzoyl-(L)-Leucine methyl ester, TFA}** A cell-permeable, prodrug form of the GGTase I inhibitor GGTI-297 (Cat. No.345882). Inhibits the processing of Rap 1A (IC_{50} = 3 µM) but has no effect on the processing of H-Ras even at concentrations of 15 µM. Inhibits PDGF-receptor tyrosine phosphorylation. Also arrests cells in the G_0/G_1 phase of the cell cycle, induces apoptosis, and enhances iNOS induction by IL-1ß.	250 µg
Gliotoxin, *Gladiocladium fimbriatum*	**371715**	**{2,3,5a,6-Tetrahydro-6-hydroxy-3(hyroxymethyl)-2-methyl-10H-3a,10a-epidithio-pyrazinol[1,2α]indole-1,4-dione}** An immunosuppressive secondary metabolite produced by several pathogenic fungi. Immunosuppressive effects are caused by blocking of membrane thiol groups. Causes apoptotic cell death in a variety of cell types including macrophages and thymocytes. Farnesyltransferase (FTase) inhibitor (IC_{50} = 1.1 µM). Reported to increase ryanodine Ca^{2+} channel activity possibly by oxidizing cysteine residues located on the ryanodine receptor. Specifically inhibits NF-κB activation in B and T cells at nanomolar concentrations.	1 mg
Histone Lysine Methyltransferase Inhibitor	**382190**	**[HTMase Inhibitor; BIX-01294; 2-(Hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-6,7-dimethoxy-N-(1-(phenylmethyl)-4-piperidinyl)-4-quinazolinamine]** A cell-permeable diazepinyl-quinazolinamine, non-SAM (S-adenosylmethionine) analog-based HMTase (histone methyltransferase) inhibitor that selectively interferes with the G9a-catalyzed H3K9me2 (histone H3 Lys9 dimethylation) modification (IC_{50} = 1.7 µM) in a reversible manner. It inhibits the GLP-catalyzed H3K9me3 only at much higher concentrartions (IC_{50} = 38 µM) and exhibits little activity against H3 methylations catalyzed by other HMTases (PRMT1, SET7/9, ESET, SUV39H1). Shown to effectively synergize with *Oct*3/4 and *Klf*4 in inducing reprogramming of primary murine fetal NPCs (Neural Progenitor Cells) into iPS (induced Pluripotent Stem) cells without additional viral transduction of *Sox2* and c-*Myc*.	5 mg
α-Hydroxyfarnesylphosphonic Acid	**390601**	**(HFPA)** A cell permeable potent, selective, and competitive inhibitor of farnesyltransferase (IC_{50} = 30 nM) in isolated enzyme assays and in whole cells. Reported to inhibit geranylgeranyltransferase I and II at much higher concentrations (IC_{50} = 35.8 and 67 µM, respectively). Induces ABA (photohormone abscisic acid) hypersensitivity of plant guard cell anion-channel activation of stomatal closing.	1 mg
L-744,832	**422720**	**{(2S)-2-[[(2S)-2-[(2S,3S)-2-[(2R)-2-Amino-3-mercaptopropyl]amino]-3-methylpentyl]oxy]-1-oxo-3-phenylpropyl]amino]-4-(methylsulfonyl)-butanoic Acid 1-Methylethyl Ester; L-744,382}** A cell-permeable potent and selective thiol-containing peptidomimetic farnesyltransferase (FTase) inhibitor with anti-tumor properties. Rapidly blocks p70S6K activation and DNA synthesis and promotes apoptosis in transgenic mice. Induces p21 expression and cell cycle arrest in the G_1 phase. Displays synergistic effect with paclitaxel and epothilones in inhibiting tumor growth. Also mimics many of the effects of Rapamycin (Cat. No.553210) and may be effective against tumors that exhibit inappropriate activation of the mTOR/p70S6K pathway.	5 mg
Manumycin A, *Streptomyces parvulus*	**444170**	An antibiotic with antitumor properties. A cell-permeable potent and selective inhibitor of farnesyltransferase (FTase; IC_{50} = 5 µM) compared to geranylgeranyltransferase I (GGTase I; IC_{50} = 180 µM). Manumycin acts as a competitive inhibitor of FTase with respect to farnesylpyrophosphate (FPP; K_i = 1.2 µM), but acts as a noncompetitive inhibitor with respect to the Ras acceptor protein. Reported to inhibit the growth and invasive activity of pancreatic cancer cells.	1 mg
Protein Arginine N-Methyltransferase Inhibitor, AMI-1	**539209**	A cell-permeable, symmetrical sulfonated urea compound that acts as a potent, specific and non-AdoMet (S-adenosyl-L-methionine, SAM)-competitive inhibitor of protein arginine N-methyltransferases (PRMTs; IC_{50} = 8.81 µM for PRMT1 and 3.03 for yeast-RMT1p) with minimal effect on lysine methyltransferases. Inhibits nuclear receptor reporter gene activation in MCF-7 cells, and HIV-1 RT polymerase (IC_{50} = 5 µM).	5 mg
Protein Arginine N-Methyltransferase Inhibitor, AMI-1	**539209**	**(PRMT Inhibitor, AMI-1)** A cell-permeable, symmetrical sulfonated urea compound that acts as a potent, specific and non-AdoMet (S-adenosyl-L-methionine, SAM)-competitive inhibitor of protein arginine N-methyltransferases (PRMTs; IC_{50} = 8.81 µM for PRMT1 and 3.03 for yeast-RMT1p) with minimal effect on lysine methyltransferases. Inhibits nuclear receptor reporter gene activation in MCF-7 cells, and HIV-1 RT polymerase (IC_{50} = 5 µM).	5 mg

Farnesyltrasferase (FTase), Geranylgeranyltransferase (GGTase), and Methyltransferase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Protein Methyltransferase Inhibitor, AMI-5	**539211**	**[A(K)MI-5; Disodium-2-(2,4,5,7-tetrabromo-3-oxido-6-oxoxanthen-9-yl)benzoate, trihydrate]** A xanthenyl compound that inhibits the activities of protein arginine methyltransferases (PRMT) Hmt1p, PRMT1/3/4/6 (IC_{50} against yeast Hmt1p & human PRMT1 = 0.78 and 1.41 µM, respectively), as well as histone lysine methyltransferases (HMTases) SET7 and DOT1 in an AdoMet/SAM- (S-adenosylmethionine) competitive manner. Although SAM-competitive inhibitors generally exhibit broad activity against and are non-selective toward most SAM-utilizing enzymes, AMI-5 is known to be inactive against at least two HMTases (Suv39H1 and Suv39H2).	50 mg
Protein Synthesis Initiation Inhibitor, NSC 119889	**539690**	**3,4,5,6-Tetrabromofluorescein** A cell-permeable, xanthenyl compound that prevents mRNA-ribosome interaction and inhibits 5'-mediated/cap-dependent initiation of protein synthesis (>95% inhibition at 50 µM in *in vitro* translation assays using Krebs, rabbit reticulocyte, or *E. coli* S30 extract).	25 mg

Glycoprotein Processing and Trafficking Inhibitors

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.

Glycoprotein Processing and Trafficking Inhibitors

Product	Cat. No.	Comments	Size
Australine, Hydrochloride, *Castanospermum australe*	**189422**	**[(1R,2R,3R,7S,7aR)-3-Hydroxymethyl-1,2,7-trihydroxypyrrolizidine]** A polyhydroxylated pyrrolizidine alkaloid that inhibits α-glucosidase, amyloglucosidase, and glucosidase I. Appears to be the first glucosidase inhibitor that is active toward glucosidase I but not glucosidase II. Inhibits glycoprotein processing at the glucosidase I step, resulting in the accumulation of glycoproteins containing $Glc_3Man_{7\text{-}9}(GlcNAc)_2$-oligosaccharides. Does not inhibit α- or ß-galactosidase, ß-glucosidase, or α- or ß-mannosidase.	1 mg
Benzyl-2-acetamido-2-deoxy-α-D-galactopyranoside	**200100**	**(Benzyl-α-GalNAc)** Used as an inhibitor of O-linked glycosylation in a variety of cell lines. Also inhibits 2,3(O)-sialyltransferase and disrupts glycoprotein targeting in HT-29 cells. Substrate for N-acetyl-ß-D-glucosaminyltransferase.	100 mg
N-(*n*-Butyl) deoxygalactonojirimycin	**203994**	A potent and selective inhibitor of α-D-galactosidase.	5 mg
N-Butyldeoxynojirimycin, Hydrochloride	**203996**	**(N-Butyl-DNJ, HCl; NB-DNJ, HCl)** 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. Shown to reversibly induce infertility in male mammals. Does not inhibit cell proliferation.	10 mg
Castanospermine, *Castanospermum australe*	**218775**	**(1S,6S,7R,8aR)-Tetrahydroxyoctahydroindolizine** Plant alkaloid inhibitor of several ß-glucosidases and α-glucosidases, including those involved in N-linked processing of glycoproteins. Resulting oligosaccharides are primarily $Glu_3Man_{7\text{-}9}(GlcNAc)_2$. Reduces bFGF induced angiogenesis in mice. Inhibits endothelial cell migration and invasion of basement membrane. Exhibits anti-viral properties. Typically used at 1-10 µg/ml.	1 mg

Glycoprotein Processing and Trafficking Inhibitors *continued*

Product	Cat. No.	Comments	Size
Conduritol B Epoxide	**234599**	**CBE** Inhibits α-glucosidase activity in mammals, snails, sweet almonds, and yeast. An irreversible, potent, and specific inhibitor of glucocerebrosidase in cultured neurons. Has also been shown to inhibit α-glucosidase from yeast and rabbit intestinal sucrase-isomaltase complex.	50 mg 100 mg
2-Deoxy-D-galactose	**259580**	Hexose analog that can be incorporated into rat gangliosides GM_2 and GD_3 in positions normally occupied by galactose. 2-Deoxy-D-galactose has been 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
Deoxygalactonojirimycin, Hydrochloride	**259544**	**(DGJ; 1,5-Dideoxy-1,5-imino-D-galactitol; Galactostatin, HCl)** Potent and selective α-galactosidase inhibitor.	5 mg
1-Deoxymannojirimycin, Hydrochloride	**260575**	**(1,5-Dideoxy-1,5-imino-D-mannitol, HCl; DMJ)** A specific α-mannosidase I inhibitor that blocks conversion of high mannose to complex oligosaccharides.	5 mg
1-Deoxynojirimycin, Hydrochloride	**260684**	**(DNJ, HCl)** A specific glucosidase inhibitor including trimming glucosidases I and II, enzymes that sequentially remove the three glucose residues from precursor Glc_3Man_9-$GlcNAc_2$ in N-linked glycan biosynthesis.	1 mg 10 mg
DL-*threo*-PDMP, Hydrochloride	**513100**	**1-Phenyl-2-decanoylamino-3-morpholino-1-propanol, HCl** PDMP closely resembles the natural sphingolipid substrate of brain glucosyltransferase and acts as a potent and competitive inhibitor of this enzyme. Blocks the outgrowth of neurites and inhibits glycolipid synthesis in cultured NIH/3T3 cells.	50 mg 100 mg
Glucagon Receptor Antagonist I	**346001**	**N-(3-Cyano-6-(1,1-dimethylpropyl)-4,5,6,7-tetrahydro-1-benzothien-2-yl)-2-ethylbutanamide** A cell-permeable thienyl-amide compound that acts as a potent, selective, and competitive antagonist of the glucagon receptor. Shown to bind to hGCGR with high affinity and prevent its interaction with glucagon (IC_{50} = 181 nM, K_{DB} = 81 nM, and *p*A2 = 7.1 in membranes prepared from CHO-hGCGR). Also suppresses glucagon-induced glycogenolysis in human primary hepatocytes and in mice (50 mg/kg, ip).	5 mg
Glucagon Receptor Antagonist II	**346003**	**2-(4-Pyridyl)-5-(4-chlorophenyl)-3-(5-bromo-2-propyloxyphenyl)pyrrole** A cell-permeable triarylpyrrole compound that acts as a selective, non-competitive, high affinity glucagon receptor antagonist (IC_{50} = 3.7 nM, 63 nM, and 60 nM for inhibition of labeled glucagon binding to human, murine, and canine glucagon receptor, respectively). Exhibits diminished antagonistic properties in the presence of Mg^{2+} (by ≥ 20-fold) and exhibits poor affinity for the rat, guinea pig, and rabbit glucagon receptors (IC_{50} > 1 µM). Does not inhibit binding of glucagon-like peptide-1 (GLP-1) to the homologous GLP-1 receptor even at concentrations as high as 10 µM. Does not affect ligand binding of a panel of other GPCRs and only weakly affects p38 kinase activity (IC_{50} = 1.44 µM). Potently inhibits glucagon-induced $GTP_{\gamma}S$ binding to $G_{\alpha}s$ (IC_{50} = 158 nM) and adenylate cyclase activation in hGLUR-CHO cells (K_b = 25 nM). Shown to be orally bioavailable in both mice and rats.	5 mg
Glucagon Receptor Antagonist, Control	**346002**	**N-(3-Cyano-6-(1,1-dimethylpropyl)-4,5,6,7-tetrahydro-1-benzothien-2-yl)-4-bromobenzamide** A cell-permeable thienyl-amide compound that serves as an inactive control for Glucagon Receptor Antagonist (Cat. No.346001). Displays weak affinity to hGCGR and is ineffective in preventing glucagon binding (20% inhibition at 10 µM in membranes prepared from CHO-hGCGR) and glucagon-, forskolin-, and GIP-induced cAMP production (10% inhibition in CHO-hGCGR cells). Only minimally suppresses glucagon-induced glycogenolysis in human primary hepatocytes.	1 mg
Glycogen Phosphorylase Inhibitor	**361515**	**1-(3-(3-(2-Chloro-4,5-difluorobenzoyl)ureido)-4-methoxyphenyl)-3-methylurea** A cell-permeable urea compound that acts as a potent and AMP-competitive inhibitor of glycogen phosphorylase (GP; IC_{50} = 53 nM). Shown to inhibit glucagon-induced glyocgenolysis both in hepatocytes (IC_{50} = 380 nM) *in vitro* and in rats (5 mg/kg, iv) *in vivo*.	1 mg
Kifunensine, *Kitasatosporia kifunense*	**422500**	A potent alkaloid inhibitor of mannosidase I. Does not affect mannosidase II and the endoplasmic reticulum α-mannosidase.	1 mg
Swainsonine, *Swainsona canescens*	**574775**	**[8aß-Indolizidine-1α,2α,8ß-triol; (1S,2S,8R,8aR)-Trihydroxyindolizidine]** Reversible active-site inhibitor of lysosomal α-mannosidase. Inhibits the growth of tumors and prevents metastasis in murine models. 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. Active *in vitro* against Gram-positive bacteria, yeasts, fungi, and viruses. Inhibits the expression of functional thrombin receptors on human T-lymphoblastoid cells. Also inhibits thrombin-induced Ca^{2+} mobilization in cells.	10 mg 50 mg

Heat Shock Protein Inhibitors

Heat shock proteins (HSPs) are a group of proteins that are expressed at higher levels when cells are exposed to higher temperatures. The upregulation of the HSPs is a key part of the heat shock response. Production of high levels of heat shock proteins can also be triggered by exposure to different kinds of environmental stress conditions, such as infection, inflammation, exposure of the cell to toxins. Depending on the level of stress, injured cells may undergo either necrosis or apoptosis. Under extreme stress conditions, when there is diminution in regulated activation of apoptotic pathways, cells undergo necrosis. At lower stress levels, cells activate their apoptotic machinery. However, at sub-lethal stress levels, cells may attempt to survive and activate a stress response system that includes a rapid induction of HSPs. HSPs interact with diverse protein substrates and assist in their folding and in the elimination of any misfolded or damaged molecules. They are transiently expressed during cell cycle to prevent differentiating cells from undergoing apoptosis. Many tumor cells have constitutively elevated levels of HSP that impart protection against cytotoxic agents thereby raising the apoptosis threshold of these cells. This abnormal expression of HSPs may lead to multi-drug resistance in aggressively growing tumors. Many HSPs, including HSP27 and HSP70, have been shown to block apoptosis. HSPs can also allow cancerous cells to escape the immunosurveillance mediated by death ligands and can render these cells resistant to chemotherapy. Hence, HSPs are fast becoming new targets for therapeutic interventions.

References
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Heat Shock Protein Inhibitors

Product	Cat. No.	Comments	Size
17-AAG	**100068**	A less toxic, potent, synthetic derivative of the ansamycin benzoquinone antibiotic Geldanamycin, *Streptomyces hygroscopicus* (Cat. No.345805) that binds to Hsp90 (EC_{50} = 7.2 µM) and regulates its function. Induces apoptosis and displays antitumor effects (IC_{50} = 4.1 nM in SKBR3 and 5.2 nM in MCF7 cells). Depletes cancer cells of erbB-1, erbB-2 (EC_{50} = 45 nM), mutant p53 (EC_{50} = 62 nM), Raf-1 (EC_{50} = 80 nM), and Akt and hence inhibits the Ras/Raf/MEK and PI3-kinase signaling pathways. Also sensitizes cancer cells to Paclitaxel (Cat. No.580555) and Doxorubicin (Cat. No.324380) and downregulates vascular endothelial growth factor expression.	500 µg
17-DMAG	**100069**	A potent antitumor analog of 17-AAG (Cat. No.100068) that binds to the ATPase site of human Hsp90α with high affinity (GI_{50} = 51 nM for 17-DMAG vs. 120 nM for 17-AAG in the NCI 60-cell panel *in vitro* activity screen), and displays excellent bioavailability and aqueous solubility.	500 µg
Geldanamycin, *Streptomyces hygroscopicus*	**345805**	A benzoquinoid antibiotic that inhibits $p60^{c\text{-}src}$ tyrosine kinase and c-*myc* gene expression in murine lymphoblastoma cells. Geldanamycin has antiproliferative and antitumor effects. Rapidly depletes $p185^{c\text{-}erbB2}$ protein tyrosine kinase in breast carcinoma cells. Binds to HSP90 and disrupts Raf1-HSP90 complex leading to destabilization of Raf1. Inhibits basal and hypoxia-induced expression of c-Jun (IC_{50} = 75 nM) and abolishes hypoxia-induced increase in c-Jun N-terminal kinase activity. Also known to selectively destabilize mutated p53 protein from a number of breast, leukemia, and prostate cell lines.	100 µg
Heat Shock Protein Inhibitor I	**373260**	A benzylidene lactam compound that blocks the induction of heat shock proteins HSP70, HSP72, and HSP105. Blocks the development of thermotolerance in a dose-dependent manner. Does not affect the thermosensitivity of nontolerant cells. Reported to be less toxic and more effective than Quercetin (Cat. No.551600); and unlike Quercetin, it does not have an affect on the activities of PKA, PKC, or PTK.	5 mg
Heat Shock Protein Inhibitor II	**373265**	A metabolite of the Heat Shock Protein Inhibitor I (Cat. No.373260) that exhibits similar *in vitro* activity.	10 mg
Hsp25 Kinase Inhibitor	**385880**	A 13-residue, cell-permeable peptide that acts as a potent and selective inhibitor of mammalian heat-shock protein (Hsp25) kinase [also called 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-competitive with respect to ATP (K_i = 134 µM).	1 mg

Heat Shock Protein Inhibitors *continued*

Product	Cat. No.	Comments	Size
HSP90 Inhibitor, CCT018159	**385920**	**4-(4-(2,3-Dihydro-1,4-benzodioxin-6-yl)-5-methyl-1H-pyrazol-3-yl)-6-ethylresorcinol** A cell-permeable pyrazoloresorcinol compound that inhibits HSP90 ATPase activity (IC_{50} = 3.2 µM and 6.6 µM against human HSP90ß and yeast HSP90, respectively) by targeting the enzyme's N-terminal ATP binding site. It exhibits no detectable effects against human Hsp70 or topoisomerase II even at concentrations as high as 100 µM and inhibits a panel of 20 commonly studied kinases only at much higher concentrations. Unlike 17-AAG (Cat. No.100068), the antitumor activity of CCT018159 is not affected by the expression of NQ01/DT-diaphorase or P-glycoprotein.	5 mg
6-Phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide	**152228**	**6-Phenylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide** A cell-permeable imidazothiadiazole compound that activates cellular transcription factor HSF1 by binding to HSP90 and disrupting its association with HSF1. Shown to induce HSF1-dependent expression of HSP70 and HSP25 and effectively block NRAGE- and p75NTR-mediated JNK activation and apoptosis in PC12 cells in a dose-dependent manner (>90% inhibition at 40 µM).	5 mg

Hexosaminidase Inhibitors

Product	Cat. No.	Comments	Size
ß-Hexosaminidase Inhibitor	**376820**	**M-31850** A cell-permeable bisnaphthalimide compound that acts as a substrate-competitive and selective inhibitor against human ß-N-acetyl hexosaminidase (IC_{50} = 6.0 and 3.1 µM for hHex A and hHex B, respectively), while exhibiting much reduced potency against Jack Bean or bacterial Hex (IC_{50} = 280 & >500 µM for JBHex & SpHex, respectively) and little or no activity against SmHex or hOGN. Shown to function as a pharmacological chaperone and effectively enhance the transport of mutant Hex alpha subunit from the ER to lysosome in cells derived from ISD and ATSD patients.	10 mg

InhibitorSelect™ Pathway Panels

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Inhibitor Signaling Pathway Panels

Product	Cat. No.	Comments	Size
InhibitorSelect™ Akt/PI 3-K/mTOR Signaling Pathway Inhibitor Panel	**124031**	A panel of 12 highly potent and selective kinase inhibitors and a negative control useful for the study of Akt/PI 3-K/mTOR signaling pathway. This panel contains the following inhibitors: 1 mg of Akt Inhibitor IV (Cat. No.124011); 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018); 5 mg of LY-294002 (Cat. No.440202); 1 mg of LY 303511 (Cat. No.440203); 5 mg of PDK1/Akt/Flt Dual Pathway Inhibitor (Cat. No.521275); 1 mg of PI-103 (Cat. No.528100); 5 mg of PI 3-Kγ Inhibitor (Cat. No.528106); 5 mg of PI 3-Kγ Inhibitor II (Cat. No.528108); 5 mg of PI 3-Kα Inhibitor IV (Cat. No.528111); 5 mg of PI 3-Kα Inhibitor VIII (Cat. No.528116); 100 µg of Rapamycin (Cat. No.553210); 500 µg of Ro-31-8220 (Cat. No.557520); and 1 mg of Wortmannin (Cat. No.681675). Also provided is 15 ml of anhydrous DMSO. Supplied with a data sheet.	1 ea

Inhibitor Signaling Pathway Panels *continued*

Product	Cat. No.	Comments	Size
InhibitorSelect™ EGFR Signaling Pathway Inhibitor Panel	**324839**	A panel containing 13 potent and selective inhibitors useful for the study of EGFR signaling pathway. This panel contains the following inhibitors: 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akt-1/2 (Cat. No.124018); 1 mg of PD 153035 (Cat. No.234490); 1 mg of EGFR Inhibitor (Cat. No.324674); 5 mg of Et-18-OCH_3 (Cat. No.341207); 5 mg of JNK Inhibitor II (Cat. No.420119); 5 mg of LY 294002 (Cat. N0.440202); 5 mg of PD 98059 (Cat. No.513000); 1 mg of PD 168393 (Cat. No.513033); 1 mg of PP2 (Cat. No.529573); 100 µg of Rapamycin (Cat. No.553210); 1 mg of SB 203580 (Cat. No.559389); 5 mg of AG 490 (Cat. No.658401) and 1 mg of ZM 336372 (Cat. No.692000). Also provided is 15 ml of anhydrous DMSO. Supplied with a data sheet.	1 ea
InhibitorSelect™ FGF Signaling Pathway Inhibitor Panel	**341612**	A panel containing 14 potent, selective, reversible and cell-permeable inhibitors useful for the study of multiple signaling pathways activated by FGF: 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018); 2 mg of EGF/FGF/PDGF Receptor Tyrosine Kinase Inhibitor (Cat. No.324841); 5 mg of ET-18-OCH3 (Cat. No.341207); 2 mg of FGF/VEGF Receptor Tyrosine Kinase Inhibitor, PD173074 (Cat. No.341607); 5 mg of FGF Receptor Tyrosine Kinase Inhibitor (Cat. No.341608); 500 µg of Gö 6983 (Cat. No.365251); 5 mg of JNK Inhibitor VIII (Cat. No.420135); 5 mg of LY 294002 (Cat. No.440202); 5 mg of PD 98059 (Cat. No.513000); 1 mg of PP2 (Cat. No.529573); 5 mg of Rac1 Inhibitor (Cat. No.553502); 10 mg of STAT3 Inhibitor III, WP1066 (Cat. No.573097); 1 mg of U0126 (Cat. No.662005); 1 mg of ZM 336372 (Cat. No.692000). Also provided with 15 ml of anhydrous DMSO (Cat. No. KP31817). Supplied with a data sheet.	1 ea
InhibitorSelect™ IGF Signaling Pathway Inhibitor Panel	**407249**	A panel containing 13 potent, selective, reversible and cell-permeable inhibitors, 1 potent, selective and reversible inhibitor, and 1 potent, selective, irreversible and cell-permeable inhibitor useful for the study of multiple signaling pathways activated by IGF: 1 mg of AG1024 (Cat. No.121767); 1 mg of Akt Inhibitor IV (Cat. No.124011); 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018); 1 mg of AMPK Inhibitor, Compound C (Cat. No.171260); 10 mg of bpVphen (Cat. No.203695); 1 mg of ERK Inhibitor, FR180204 (Cat. No.328007); 5 mg of GSK-3ß Inhibitor VIII (Cat. No.361549); 1 mg of IGF-1R Inhibitor, PPP (Cat. No.407247); 5 mg of NBI-31772 (Cat. No.479803); 5 mg of PD 98059 (Cat. No.513000); 1 mg of PI-103 (Cat. No.528100); 500 µg of PKCß Inhibitor (Cat. No.539654); 100 µg of Rapamycin (Cat. No.553210); 1 mg of RSK Inhibitor, SL0101 (Cat. No.559285); 1 mg of ZM 336372 (Cat. No.692000). Also provided with 15 ml of anhydrous DMSO (Cat. No. KP31817). Supplied with a data sheet.	1 ea
InhibitorSelect™ JAK/STAT Signaling Pathway Inhibitor Panel	**420138**	A convenient panel containing 13 potent and selective inhibitors useful for the study of JAK/STAT signaling pathway. This panel contains the following inhibitors: 1 mg of Indirubin Derivative E804 (Cat. No.402081); 500 µg of JAK Inhibitor I (Cat. No.420099); 25 mg of JAK2 Inhibitor II (Cat. No.420132); 5 mg of LY 294002 (Cat. No.440202); 1 mg of PD 153035 (Cat. No.234490); 1 mg of PP2 (Cat. No.529573); 50 mg of SHP1/2 PTPase Inhibitor, NSC-87877 (Cat. No.565851); 1 mg of STAT3 Inhibitor Peptide, Cell-Permeable (Cat. No.573096); 10 mg of STAT3 Inhibitor III, WP1066 (Cat. No.573097); 25 mg of STAT3 Inhibitor V, Stattic (Cat. No.573099); 10 mg of STAT5 Inhibitior (Cat. No.573108); 5 mg of AG490 (Cat. No.658401) and 1 mg of U0126 (Cat. No.662005). Also provided with 15 ml of anhydrous DMSO.	1 ea
InhibitorSelect™ MAP Kinase Signaling Pathway Inhibitor Panel	**444189**	A panel of 12 potent and selective inhibitors useful for the study of MAP kinase signaling pathway. This panel contains the following inhibitors: 1 mg of ERK Inhibitor II, FR180204 (Cat. No.328007); 5 mg of JNK Inhibitor II (Cat. No.420119); 5 mg of JNK Inhibitor IX (Cat. No.420136); 1 mg of MEK1/2 Inhibitor (Cat. No.444939); 5 mg of MNK1 Inhibitor (Cat. No.454861); 5 mg of MK2a Inhibitor (Cat. No.475863); 1 mg of p38 MAP Kinase Inhibitor V (Cat. No.506156); 5 mg of PD 98059 (Cat. No.513000); 1 mg of Raf Kinase Inhibitor IV (Cat. No.553014); 1 mg of SB 203580 (Cat. No.559389); 1 mg of Tpl2 Kinase Inhibitor (Cat. No.616373) and 1 mg of ZM 336372 (Cat. No.692000). Also provided with 15 ml of anhydrous DMSO.	1 ea
InhibitorSelect™ NF-κB Signaling Pathway Inhibitor Panel	**481487**	A panel containing 14 potent and selective inhibitors useful for the study of NF-κB signaling pathway. This panel contains the following inhibitors: 10 mg of BAY 11-7082 (Cat. No.196870); 1 mg of IKK Inhibitor VII (Cat. No.401486); 5 mg of Interleukin1-Receptor-Associated-Kinase-1/4 Inhibitor (Cat. No.407601); 10 mg of Histone Acetyltransferase Inhibitor II (Cat. No.382110); 5 mg of MG-132 (Cat. No.474790); 500 µg of NEMO-Binding Domain-Binding Peptide, Cell-Permeable (Cat. No.480025); 500 µg of NF-κB SN50, Cell-Permeable Inhibitor Peptide (Cat. No.481480); 5 mg of PD 98059 (Cat. No.513000); 5 mg of PDK1/Akt/Flt Dual Pathway Inhibitor (Cat. No.521275); 1 mg of Trichostatin A, *Streptomyces* sp. (Cat. No.647925); 1 mg of TIRAP Inhibitor Peptide, Cell-Permeable (Cat. No.613570), 1 mg of Tpl2 Kinase Inhibitor (Cat. No.616373), 1 mg of (5*Z*)-7-Oxozeaenol, *Curvularia* sp. (Cat. No.499610), and 5 mg of JNK Inhibitor II (Cat. No.420119). Also provided with 15 ml of anhydrous DMSO.	1 ea

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Inhibitor Signaling Pathway Panels *continued*

Product	Cat. No.	Comments	Size
InhibitorSelect™ VEGF Signaling Pathway Inhibitor Panel	**676502**	A panel containing 15 potent, selective, reversible and cell-permeable inhibitors useful for the study of multiple signaling pathways activated by VEGF: 1 mg of Akt Inhibitor VIII, Isozyme-Selective, Akti-1/2 (Cat. No.124018); 1 mg of Calcineurin Autoinhibitory Peptide, Cell-permeable (Cat. No.207001); 5 mg of ET-18-OCH3 (Cat. No.341207); 500 µg of Go 6983 (Cat. No.365251); 100 mg of N^G-Nitro-L-arginine Methyl Ester, Hydrochloride (Cat. No.483125); 5 mg of p21-Activated Kinase Inhibitor III, IPA-3 (Cat. No.506106); 500 µg of cPLA2α Inhibitor (Cat. No.525143); 1 mg of PI-103 (Cat. No.528100); 1 mg of PP2 (Cat. No.529573); 1 mg of SB 203580 (Cat. No.559389); 1 mg of U0126 (Cat. No.662005); 1 mg of VEGFR Tyrosine Kinase Inhibitor III, KRN633 (Cat. No.676482), 5 mg of VEGFR2 Kinase Inhibitor VI, Ki8751 (Cat. No.676484); 1 mg of VEGFR2 Kinase Inhibitor III, SU5416 (Cat. No.676487); 1 mg of ZM 336372 (Cat. No.692000). Also provided with 15 ml of anhydrous DMSO (Cat. No. KP31817). Supplied with a data sheet.	1 ea
InhibitorSelect™ Wnt Signaling Pathway Inhibitor Panel	**681666**	A panel containing 18 potent and selective inhibitors useful for the study of the Wnt signaling pathway. This panel contains the following inhibitors: 1 mg of Casein Kinase I Inhibitor, D4476 (Cat. No.218696); 5 mg Casein Kinase II Inhibitor III, TBCA (Cat. No.218710); 10 mg of ß-Catenin/ Tcf Inhibitor, FH535 (Cat. No.219330); 1 mg of GSK-3 Inhibitor IX (Cat. No.361550); 1 mg of PKG Iα Inhibitor, Cell-Permeable (Cat. No.370655); 1 mg of H-89, Dihydrochloride (Cat. No.371963); 100 µg of K-252a, *Nocardiopsis* sp. (Cat. No.420298); 5 mg of JNK Inhibitor II (Cat. No.420119); 1 mg of KN-93 (Cat. No.422708); 5 mg of LY 294002 (Cat. No.440202); 1 mg of (5Z)-7-Oxozeaenol, *Curvularia* (Cat. No.499610); 1 mg of PP2 (Cat. No.529573); 100 µg of Rapamycin (Cat. No.553210); 1 mg of SB 202190 (Cat. No.559388); 1 mg of U0126 (Cat. No.662005). Also provided with 15 ml of anhydrous DMSO (Cat. No. KP31817). Supplied with a data sheet.	1 ea

Hypoxia-Inducable Factor Inhibitors

Product	Cat. No.	Comments	Size
HIF-1 Inhibitor	**400083**	**3-(2-(4-Adamantan-1-yl-phenoxy)-acetylamino)-4-hydroxybenzoic acid methyl ester, Hypoxia-Inducible Factor-1 Inhibitor** A cell-permeable amidophenolic compound that inhibits hypoxia-induced HIF-1 transcription activity (IC_{50} = 0.7 and 2.6 µM using AGS and Hep3B cells, respectively, in a reporter assay) by selectively blocking the hypoxia-induced accumulation of cellular HIF-1α protein, while exhibiting no apparent effect on the cellular level of HIF-1α mRNA or that of HIF-1ß protein.	10 mg

Luciferase Inhibitors

Product	Cat. No.	Comments	Size
4-(1,3-Benzothiazol-2-yl)-N,N-dimethylaniline	**119114**	**4-(1,3-Benzothiazol-2-yl)-N,N-dimethylaniline** A 2-arylbenzothiazole compound that acts as an inhibitor against the ATP-dependent *Photinus pyralis* (*lucPpy*) and *Photuris pennsylvanica* (*lucPpe*) luciferase activity (IC_{50} = 0.2 and 0.32 µM, respectively, with 10 µM ATP, 10 µM luciferin, and 10 nM respective enzyme). Unlike Luciferase Inhibitor I (Cat. No.119113), Luciferase Inhibitor II is competitive with respect to luciferin and exhibits reduced potency against *lucPpe*-based commercial luciferase-luciferin formulations with high luciferin concentration (IC_{50} = 10 µM against Promega's Kinase-Glo®; ineffective against Kinase-Glo® Plus and Kinase-Glo® Max; at a 3-fold formulation dilution and 6.77 µM ATP).	5 mg
2-(5-(2-Methoxyphenyl)-1,2,4-oxadiazol-3-yl)pyridine	**119113**	**2-(5-(2-Methoxyphenyl)-1,2,4-oxadiazol-3-yl)pyridine** A 3,5-diaryl-oxadiazole compound that acts as an inhibitor against the ATP-dependent *Photuris pennsylvanica* (*lucPpe*) and *Photinus pyralis* (*lucPpy*) luciferase activity (IC_{50} = 0.08 and 2.8 µM, respectively, with 10 µM ATP, 10 µM luciferin, and 10 nM respective enzyme) and effectively inhibits *lucPpe*-based commercial luciferase-luciferin formulations (IC_{50} = 5, 13.5, and 12.7 µM against Promega's Kinase-Glo®, Kinase-Glo® Plus, and Kinase-Glo® Max, respectively, at a 3-fold formulation dilution and 6.77 µM ATP). Unlike Luciferase Inhibitor II (Cat. No.119114), Luciferase Inhibitor I is noncompetitive with respect to either luciferin or ATP.	5 mg

Membrane Traffic Inhibitors

Product	Cat. No.	Comments	Size
Membrane Traffic Inhibitor, A5	**444805**	**A5, 1-(4-(4-(E-2-Methyl-2-butenyl)piperazinyl)phenyl)ethanone, HCl** A cell-permeable piperazinyl compound that specifically blocks clathrin adaptor complex AP-1-dependent traffic between trans-Golgi network (TGN) and endosomes in budding yeast, while exhibiting little effects against other trafficking pathways involving TGN and endosomes. Inhibits growth of yeast cells lacking complementary GGA1/2 adaptor proteins (EC_{50} = 50 µM), but not wild-type or AP-1-deficient cells even at concentrations as high as 300 µM. A5 presumably acts at a stage after AP-1 membrane recruitment as evidenced by an enhanced AP-1 perinuclear localization upon A5 treatment of HeLa cells.	10 mg

Microtubule Assembly Inhibitors

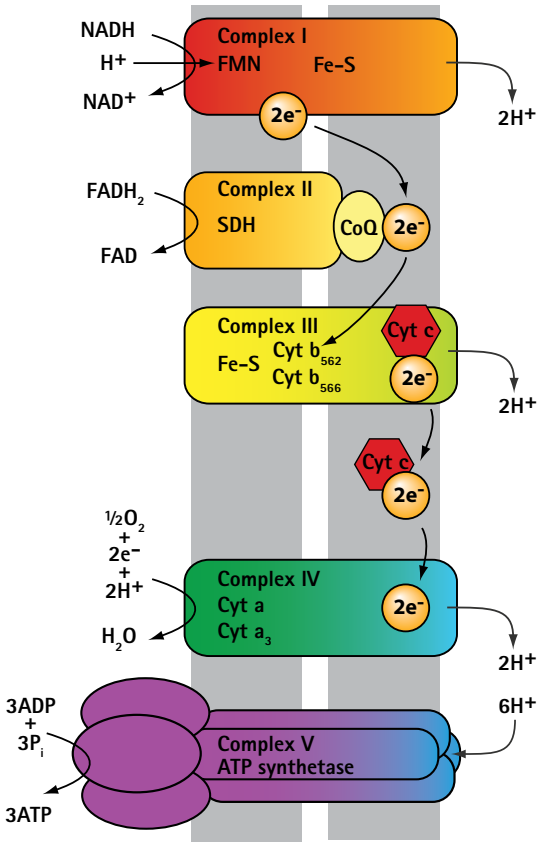
Product	Cat. No.	Comments	Size
Tubulin Polymerization Inhibitor II	654164	**(E)-1,3-Dihydro-6-methoxy-3-(3,4,5-trimethoxybenzylidene)-1H-indol-2-one** A cell-permeable, SU5416- (Cat. Nos.676487 and676498) derived combretastatin A-4 analog that acts as an effective anti-microtubule agent (IC_{50} = 4.5 µM in inhibiting polymerization of purified porcine brain tubulin) and displays extremely potent anti-proliferative activity towards various cancer cell lines (GI_{50} < 10 nM for 46 lines among a 53 NCI panel tested).	5 mg

Mitochondrial Function Inhibitors

In addition to being the energy generators in the cell, mitochondria play an important role in cell survival and cell death. In fact, any abnormality in the mitochondrial energy generation machinery can lead to cell death. Mitochondria are highly vulnerable to inhibition or uncoupling of the energy harnessing process and their structural and functional characteristics provide a number of primary targets for xenobiotic-induced bioenergetic failure. Inhibitors of mitochondrial function include compounds that act as electron transport inhibitors, uncouplers of oxidative phosphorylation, respiratory chain inhibitors, phosphorylation inhibitors, ionophores, and Krebs cycle inhibitors. The study of mitochondrial metabolism using these compounds has led to the identification of bioenergetic control points for cell replication, cell differentiation, and cell death. Use of specific inhibitors has also helped to distinguish the electron transport system from the phosphorylation system and define the sequence of redox carriers along the respiratory chain. Five different enzyme complexes have been recognized in the mitochondria. Complexes I, II, III, and IV are the electron transfer complexes, whereas complex V is an energy-conserving complex. It catalyzes ATP-P_i exchange and ATP hydrolysis.

Electron transport inhibitors act by preventing the passage of electrons from one carrier to the next. Irreversible inhibitors may cause a complete stoppage of respiration, whereas competitive inhibitors may allow some oxygen consumption and passage of electrons, but the conditions are not optimum to maintain a chemiosmotic gradient. Hence, the addition of ADP does not affect respiration. Electron transport system (ETS) accepts energy from carriers in the mitochondrial matrix and stores it to a form that can be used to phosphorylate ADP. NAD and FAD are the two energy carriers that donate energy to ETS. NAD carries energy to complex I (NADH-Coenzyme Q reductase) of the electron transport chain, whereas FAD is a part of the succinate dehydrogenase complex (complex II).

Uncouplers of oxidative phosphorylation, such as CCCP and 2,4-dintirophenol, inhibit mitochondrial function by abolishing the obligatory linkage between the respiratory chain and the phosphorylation system in intact mitochondria. Here the electron transport system is uninhibited due to complete and irreversible dissipation of the chemiosmotic gradient.



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Mitochondrial Function Inhibitors

Product	Cat. No.	Comments	Size
Atractyloside, Dipotassium Salt, *Atractylis gummifera*	**189300**	**(ATR, 2K)** Toxic compound originally isolated from the Mediterranean thistle *Atractylis gummifera*. Acts as an ADP/ATP translocase (AAT) inhibitor. Also causes the release of cytochrome *c* from mitochondria.	50 mg
Bongkrekic Acid, Triammonium Salt	**203671**	**(BA, 3NH4; 3-Carboxymethyl-17-methoxy-6,18,21-trimethyldocosa-2,4,8,12,18,20-heptaenedioic Acid)** Acts as a ligand of the adenine nucleotide translocator. A potent inhibitor of mitochondrial megachannel (permeability transition pore). Significantly reduces signs of apoptosis induced by nitric oxide. Prevents the apoptotic breakdown of the inner mitochondrial transmembrane potential ($\Delta\Psi_m$), as well as a number of other phenomena linked to apoptosis.	500 µg
Carbonyl Cyanide *m*-Chlorophenylhydrazone	**215911**	**(CCCP)** Protonophore. Uncoupling agent for oxidative phosphorylation that inhibits mitochondrial function. Approximately 100 times more effective than 2,4-dinitrophenol. Binds with cytochrome c oxidase with high affinity (K_d = 270 nM). Inhibits transport processes and depresses growth.	250 mg
Carboxyatractyloside, Potassium Salt, *Xanthium sibiricum*	**216201**	**Carboxyatractyloside, Potassium Salt** Toxic compound isolated from the plant *Xanthium sibiricum*. A highly selective and potent inhibitor of adenine nucleotide translocator (ANT) (K_i < 10 nM) and inducer of permeability transition pore opening. Stabilizes the nucleoside binding site of ANT on the cytoplasmic side of the inner membrane and blocks the exchange of matrix ATP and cytoplasmic ADP. Does not affect the activity of mitochondrial multiple conductance channel (MCC).	2 mg 5 mg
CGP-37157	**220005**	**[7-Chloro-5-(2-chlorophenyl)-1,5-dihydro-4,1-benzothiazepin-2(3H)-one]** A cell-permeable benzothiazepine derivative of clonazepam that acts as a specific and potent inhibitor of the mitochondrial Na^+/Ca^{2+} exchanger (IC_{50} = 360 nM). Enhances the export of Ca^{2+} from isolated mitochondria. Also reported to directly inhibit voltage-gated Ca^{2+} channels.	5 mg
(-)-Deguelin, *Mundulea sericea*	**252740**	A cell-permeable rotenoid compound that displays anti-proliferative properties. Potently inhibits mitochondrial bioenergetics (IC_{50} = 6.9 nM for NADH:ubiquinone oxidoreductase activity in bovine heart ETP) and promotes mitochondrial permeability transition. Blocks phorbol ester-induced ornithine decarboxylase activity in MCF-7 cells (IC_{50} = 11 nM) and induces apoptosis and cell cycle arrest. Selectively blocks Akt activation with minimal effects on MAPK signaling. Also shown to activate AMPK activity and inhibit COX2 expression.	5 mg
F16	**341246**	A cell-permeable, fluorogenic, delocalized lipophilic cationic compound that acts as a mitochondrial toxin and possesses the dual ability to induce apoptosis as well as necrosis in tumor cells. Preferentially accumulates in mitochondria, inhibits oxidative phosphorylation and causes mitochondrial transmembrane depolarization. The incorporation and localization of F16 can be easily monitored by its fluorescence property.	25 mg
Hexokinase II VDAC Binding Domain Peptide, Cell-Permeable	**376816**	**(H-RQIKIWFQNRRMKWKK-MIASHLLAYFFTELN-NH_2; HXK2VBD-cpm)** A cell-permeable peptide analog of Hexokinase II VDAC binding domain peptide (Cat. No.376815). The internalization domain of the Antennapedia homeoprotein is fused to the methionine amino terminal. Shown to completely detach and translocate HXK2 from mitochondria to the cytosol in HeLa cells at 100 µM. Does not induce Bax translocation or cytochrome *c* release when used alone. However, it markedly sensitizes cells to cytochrome *c* release and to the induction of apoptosis when used in combination with a Bax-dependent apoptosis inducer, Indomethacin (Cat. No. 405268).	1 mg
m-Iodobenzylguanidine, Hemi	**407721**	**3-Iodobenzylguanidine, Hemisulfate** A cell-permeable norepinephrine analog that displays antiproliferative and proapoptotic properties. Reported to competitively inhibit arginine-dependent mono-ADP-ribosylation, impair mitochondrial respiration, stimulate glycolysis, and prevent terminal differentiation of skeletal myoblasts reversibly. Readily taken up by tissues rich in sympathetic neurons and neuroendocrine neoplasm via norepinephrine transporters (NET). Inhibits the phosphorylation of the Rho effector, PRK1/2 with no effect on the stimulation of MAP and PI3-kinases.	10 mg

Mitochondrial Function Inhibitors *continued*

Product	Cat. No.	Comments	Size
Mitochondrial Division Inhibitor, mdivi-1	**475856**	**3-(2,4-Dichloro-5-methoxy-phenyl)-2-thioxo-1H-quinazolin-4-one, Mitochondrial Division Dnm1/Drp1 ATPase Inhibitor** A cell-permeable quinazolinone compound that inhibits yeast (Dnm1) and mammalian (Drp1) division DRPs (dynamin-related GTPases) and effectively induces mitochondrial fusion into net-like structures (IC_{50} = 10 and 50 µM in yeast and COS cultures, respectively) in a reversible manner. Cell-free studies indicate that mdivi-1 blocks Dnm1 ATPase activity (IC_{50} < 10 µM) and self-assembly by an allosteric modulation-based mechanism. Mdivi-1 is shown to effectively suppress STS- (Cat. Nos.569396 and569397) as well as C8-Bid-induced MOMP (Mitochondrial Outer Membrane Permeabilization) in HeLa cultures and in cell-free murine liver mitochondria preparations, respectively, as assessed by cytochrome C release.	10 mg
Oligomycin	**495455**	A mixture of A, B, and C isomers. A macrolide antibiotic that inhibits membrane-bound mitochondrial ATPase (F_1), preventing phosphoryl group transfer. Induces apoptosis in cultured human lymphoblastoid and other mammalian cells.	10 mg
Rotenone	**557368**	A mitochondrial toxin and a potent, reversible, and competitive inhibitor of complex I (NADH-CoQ reductase) of the respiratory chain. Also inhibits cellular proliferation in mouse liver.	1 g
Ru360	**557440**	**[(m)[$(HCO_2)(NH_3)4Ru]_2OCl_3$]** A cell-permeable oxygen-bridged dinuclear ruthenium amine complex that has been shown to bind to mitochondria with high affinity (K_d = 340 pM). Specifically blocks Ca^{2+} uptake into mitochondria *in vitro* (IC_{50} = 184 pM) and *in situ* in intact myocytes (complete block after incubation with ~10 µM of Ru360 for 30 min). Does not affect other cellular Ca^{2+} transport processes involved in cardiac muscle contraction, even at micromolar levels.	500 µg 1 mg 1 set
Valinomycin, *Streptomyces fulvissimus*	**676377**	A cyclododecadepsi-peptide ionophore antibiotic. Potassium ionophore of the mobile ion-carrier type that transports alkali metal ions across artificial or biological lipid membranes. Induces K^+ conductivity in cell membranes at concentrations as low as 10^{-8} M. Often used in membrane electrode systems for determining K^+ concentration. Uncouples oxidative phosphorylation by binding to sites on membranes rich in sulfhydryl groups. Induces apoptosis in murine thymocytes. Also reported to inhibit NGF-induced neuronal differentiation.	25 mg 100 mg

Ornithine Decarboxylase Inhibitors

Product	Cat. No.	Comments	Size
Ornithine Decarboxylase Inhibitor	**497985**	**[POB; ODC Inhibitor; N-(4'-Pyridoxyl)-Ornithine(BOC)-OMe]** A cell-permeable pyridoxyl-ornithine compound that acts as an effective analog of the transition state coenzyme-substrate adduct during orthithine decarboxylase-(ODC) catalyzed conversion of L-orthithine to Pultrescine. POB is typically 5- to 10-fold more potent than DFMO (Cat. No.288500) in inhibiting intracellular ODC activity and tumor cell growth in cultures, while exhibiting little effect against the growth of nontumorigenic human aortic smooth muscle cells.	10 mg

Peptidylpropyl cis-trans Isomerase Inhibitors

Product	Cat. No.	Comments	Size
PPIase-Parvulin Inhibitor	**529627**	**Diethyl-1,3,6,8-tetrahydro-1,3,6,8-tetraoxobenzo[lmn][3,8]phenanthroline-2,7-diacetate** A cell-permeable napthalenetetracarboxylic-bisimide compound that displays anti-proliferative properties (IC_{50} cis-trans isomerase) activity (IC_{50} = ~ 1.5 µM). Does not bind to DNA or functions as a topoisomerase I inhibitor.	10 mg

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Phosphodiesterase Inhibitors

cAMP and cGMP, two important second messengers molecules are hydrolyzed by phosphodiesterases (PDEs) in the cell, leading to cessation of cAMP and cGMP-dependent effects. PDEs comprise a large group of enzymes organized into 11 distinct families based on their biochemical and molecular properties. Many of these isozymes are differently expressed and regulated in different cells and exhibit distinct selectivity for cAMP and cGMP. PDEs contain three functional domains: a regulatory N-terminus, a central catalytic domain, and a regulatory C- terminus. All isozymes exhibit significant homology in their catalytic domain. The N- and C-terminal domains also display moderate homology within families and impart specific characteristics to different subtypes. The N-terminus is involved in allosteric regulation and membrane targeting. The C-terminus is believed to be involved in dimerization and possess docking sites for PDEspecific kinases.

Due to their involvement in inflammation, asthma, and cardiovascular complications, erectile dysfunctions, PDEs are considered to be attractive targets for pharmacological intervention. Erectile dysfunction is a common multi-factorial complication of diabetes mellitus and PDE V inhibitor therapy has been found to be effective in special clinical populations, such as those with prostate cancer, diabetes, and cardiovascular disease.

Classification of Phosphodiesterases

PDE	Regulatory Mechanism	Tissue Distribution
I	Ca^{2+}/CaM-stimulated	Heart, brain, lung, smooth muscle
II	cGMP-stimulated	Adrenals, heart, lung, liver, platelets
III	cGMP-inhibited,	Heart, lung, liver, platelets, adipose tissue
IV	cAMP-specific	Kidney, brain, liver, lung, Sertoli cells
V	cGMP-specific	Lung, platelets, smooth muscle
VI	Photoreceptor cGMP-specific	Photoreceptors
VII	cAMP-specific, high-affinity, rolipram-insensitive	Skeletal muscle, heart, kidney, brain, pancreas, T cells
VIII	cAMP-selective, IBMX- insensitive	Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T cells
IX	cGMP-selective, IBMX insensitive	Kidney, liver, lung, brain
X	cGMP-sensitive	Testes, brain
XI	cGMP-sensitive, dual- specificity	Skeletal muscle, prostrate, kidney, liver, pituitary, salivary glands, testes

Phosphodiesterase Inhibitors

Product	Cat. No.	Comments	Size
Calmidazolium Chloride	**208665**	**(Compound R 24571)** A cell-permeable calmodulin antagonist. At least 150 times more potent than Trifluoperazine (Cat. No.642150) as an inhibitor of brain calmodulin-dependent phosphodiesterase (IC_{50} = 10 nM). An inhibitor of voltage-gated Ca^{2+} channels. Stimulates the release of nitric oxide in neuroblastoma cells. Also acts as a strong non-competitive inhibitor of skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase (K_i = 60 nM). Known to prolong cardiac refractoriness *in vivo*.	10 mg
Chlorpromazine, Hydrochloride	**215921**	**{2-Chloro-10-[3'-(dimethylamino)propyl]phenothiazine, HCl}** Inhibits calmodulin-dependent stimulation of cyclic nucleotide phosphodiesterase (IC_{50} = 17 µM). Acts as a peripheral vasodilator. Acts as an inhibitor of lysosomal sphingomyelinase and of TNF-α production. Inhibits nitric oxide synthase (NOS) in mouse brain and prevents lipopolysaccharide induction of NOS in murine lung. Shown to potently and specifically inhibit KSP/Eg5 (IC_{50} < 10 µM), and PLA2.	500 mg
Cilostamide	**231085**	**[N-Cyclohexyl-N-methyl-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide; OPC 3689]** A cell-permeable selective inhibitor of cGMP-inhibited phosphodiesterase (PDE III; IC_{50} = 70 nM).	10 mg
Denbufylline	**253500**	**[1,3-Di-*n*-butyl-7-(2'-oxopropyl)xanthine]** A cell-permeable xanthine derivative that acts as a selective inhibitor of phosphodiesterase IV (PDE IV; K_i = ~ 1 µM). Possesses bronchodilatory properties. Displays negative inotropic effect by acting on a verapamil-sensitive site of the calcium channel in guinea pig ventricle papillary muscle independently of its PDE inhibitory activity.	5 mg
Dipyridamole	**322328**	A cell-permeable, selective inhibitor of cGMP phosphodiesterase (PDE V; IC_{50} = 900 nM). A potent ectonucleosidase inhibitor that also blocks nucleoside transport into mammalian cells. Reduces the release of acetylcholine.	100 mg
EHNA, Hydrochloride	**324630**	**[*erythro*-9-(2-Hydroxy-3-nonyl)adenine, HCl]** A cell-permeable, potent inhibitor of phosphodiesterase II (PDE II) (IC_{50} = 800 nM). Does not inhibit other PDE isozymes (IC_{50} > 100 µM). Inhibits the retrograde transport motor, dynein. Also inhibits adenosine deaminase (K_i = 4 nM).	10 mg
3-Isobutyl-1-methylxanthine	**410957**	**(IBMX)** A cell-permeable, non-specific inhibitor of cAMP and cGMP phosphodiesterases (IC_{50} = 2-50 µM). Also acts as an adenosine receptor antagonist. Reported to inhibit TNF-α expression in adipocyte precursor cells.	250 mg 1 g
8-Methoxymethyl-3-isobutyl-1-methylxanthine	**454202**	**(8-Methoxymethyl-IBMX)** A cell-permeable selective inhibitor of Ca^{2+}-calmodulin-dependent phosphodiesterase (PDE I; IC_{50} = 4 µM).	10 mg
4-{[3',4'-(Methylenedioxy)benzyl]amino}-6-methoxyquinazoline	**475250**	Potent and specific inhibitor of cGMP-specific phosphodiesterase (PDE V; IC_{50} = 230 nM). Elevates the intracellular cGMP level without causing any change in the cAMP level in isolated porcine coronary arteries. Has no effect on other PDE isozymes.	1 mg
Milrinone	**475840**	**[1,6-Dihydro-2-methyl-6-oxo-(3,4'-bipyridine)-5-carbonitrile]** A cell-permeable, selective inhibitor of cGMP-inhibited phosphodiesterase (PDE III; IC_{50} = 300 nM). Has positive chronotropic, inotropic, and vasodilatory effects on the heart.	10 mg
MY-5445	**474925**	**[1-(3-Chlorophenylamino)-4-phenylphthalazine]** A cell-permeable, selective inhibitor of cGMP-specific phosphodiesterase (PDE V; IC_{50} = 600 nM).	10 mg
Phosphodiesterase 4 Inhibitor	**524717**	**[3,5-Dimethyl-1-(3-nitrophenyl)-1H-pyrazole-4-carboxylic acid ethyl ester]** A pyrazole compound that acts as a high-affinity active site binding inhibitor of phosphodiesterases IVB and IVD (IC_{50} = 33 nM and 21 nM). Shown to be much more potent than Rolipram (Cat. No.557330; IC_{50} = 570 nM and 1.1 µM for PDEIVB and PDEIVD), respectively and display greater selectivity over PDEIB, PDEIIA, PDEIIIB, PDEVA, PDEVIIB, PDEVIIIA, PDEIXA and PDEXIA (IC_{50} > 30 µM) and minimally inhibit PDEXA with an IC_{50} of 6.9 µM.	10 mg
Phosphodiesterase Inhibitor Set I	**524718**	**PDE Inhibitor Set** A convenient set of inhibitors that are selective for PDE types I, III, IV, and V. 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-methoxyquinazoline (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. Supplied with data sheet.	1 set

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Phosphodiesterase Inhibitors *continued*

Product	Cat. No.	Comments	Size
Ro-20-1724	**557502**	**[4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone]** A cell-permeable, selective inhibitor of cAMP-specific phosphodiesterase (PDE IV; IC_{50} = 2 µM). Inhibits superoxide generation and arachidonic-induced platelet aggregation. Also inhibits fMLP-induced neutrophil adhesion to vascular endothelial cells.	100 mg
Rolipram	**557330**	**{4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone}** A cell-permeable, selective inhibitor of cAMP-specific phosphodiesterase (PDE IV; IC_{50} = 800 nM). A rolipram-insensitive PDE IV subtype is also known to exist. Also inhibits NF-κB and NFAT activation in Jurkat and primary T cells.	5 mg
Trequinsin, Hydrochloride	**382425**	**[9,10-Dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido-(6,1-a)-isoquinolin-4-one, HCl; HL 725]** Extremely potent and cell-permeable inhibitor of cGMP-inhibited phosphodiesterase (IC_{50} = 300 pM) and platelet aggregation *in vitro*. Potentiates adenosine-stimulated cAMP accumulation.	10 mg
W-12, Hydrochloride	**681635**	**[N-(4-Aminobutyl)-2-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 300 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 260 µM).	1 mg
W-13, Hydrochloride	**681636**	**[N-(4-Aminobutyl)-5-chloro-2-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 58 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 68 µM).	1 mg
W-5, Hydrochloride	**681625**	**[N-(6-Aminohexyl)-1-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 230 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 240 µM).	1 mg
W-7, Hydrochloride	**681629**	**[N-(6-Aminohexyl)-5-chloro-1-naphthalenesulfonamide, HCl]** A cell-permeable and reversible calmodulin antagonist that inhibits myosin light chain kinase (IC_{50} = 51 µM) and Ca^{2+}-calmodulin-dependent phosphodiesterase (IC_{50} = 28 µM).	10 mg
Zaprinast	**684500**	**{1,4-Dihydro-5-(2-propoxyphenyl)-7H-1,2,3-triazolo [4,5-d]pyrimidine-7-one; M&B22948}** A cell-permeable, selective inhibitor of cGMP-specific phosphodiesterase (PDE V; IC_{50} = 450 nM). Inhibits PDE IX at higher concentration (IC_{50} = 35 µM). Also known to increase cGMP levels in spontaneously hypertensive rat (SHR) plasma and reverse nitroglycerin tolerance *in vitro*. Enhances the vasodilatory effects of nitric oxide.	25 mg

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 believed 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 automodi- fication 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 which are 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 pADPr 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**	**[Adenosine 5'-diphosphate (Hydroxymethyl)pyrrolidinediol, NH_4]** An amino analog of ADP-ribose that acts as a highly potent, noncompetitive, and specific inhibitor of poly(ADP-ribose) glycohydrolase (PARG; IC_{50} = 120 nM). Does not affect the activities of either poly(ADP-ribose) polymerase (PARP) or NAD:arginine mono(ADP-ribosyl)-transferase A even at 1 mM concentration. Also acts as an inhibitor of NAD glycohydrolase from *Bungarus fasciatus* venom at much higher concentrations (IC_{50} = 260 µM). Note: 1 set = 5 x 60 µg.	60 µg 1 set
4-Amino-1,8-naphthalimide	**164585**	**(4-ANI)** A potent, cell-permeable poly(ADP-ribose) polymerase (PARP) inhibitor (IC_{50}= 180 nM *in vitro*) and radiation sensitizer. Reduces ischemia-reperfusion injury in the heart and skeletal muscle.	100 mg
3-Aminobenzamide	**165350**	**(3-ABA)** A cell-permeable anti-proliferative agent that acts as an inhibitor of poly(ADP-ribose) polymerase (PARP). Has minimal effect on bacterial toxin-mediated ADP-ribosylation. An inhibitor of UV-induced apoptosis. Also strongly inhibits K562 target cell killing by human effector natural killer cells.	100 mg
DPQ	**300270**	**{3,4-Dihydro-5[4-(1-piperindinyl)butoxy]-1(2H)-isoquinoline}** A potent and selective inhibitor of poly(ADP-ribose) polymerase (PARP; IC_{50} = 40 nM). Significantly reduces infarcet volume in rat focual cerebrale ischemia model.	1 mg
EB-47	**324473**	A cell-permeable, adenosine-substituted, isoindolinone compound that acts as a potent inhibitor of PARP-1 (IC_{50} = 45 nM). Shown to offer cytoprotective effects against oxidative damage in cells and in *in vivo* models of reperfusion injury and inflammation.	1 mg
5-Iodo-6-amino-1,2-benzopyrone	**407850**	**(INH_2BP)** A cell-permeable poly(ADP-ribose) polymerase (PARP) inhibitor. Offers protection against peroxynitrite and hydroxyl radicals *in vitro* and *in vivo* and abrogates peroxynitrite-induced mitochondrial transmembrane potential ($\Delta\Psi_m$) reduction. Also exhibits malignant phenotype reversal in cancer cells and inhibits HIV-1 IIIb replication *in vitro*.	5 mg
1,5-Isoquinolinediol	**419800**	**[1,5-Dihydroxyisoquinoline; 5-Hydroxy-1(2H)-isoquinoline]** A potent, cell-permeable inhibitor of poly(ADP-ribose) polymerase (PARS; IC_{50} = 390 nM). Blocks nitric oxide-induced neuronal toxicity.	5 mg
NU1025	**493800**	**(8-Hydroxy-2-methylquinazoline-4-one)** A potent inhibitor poly(ADP-ribose) polymerase (PARP; IC_{50} = 0.40 µM). Has been shown to potentiate the cytotoxicity of the DNA-methylating agent MTIC [5-(3-N-methyltriazen-1-yl)-imidazole-4-carboxamide] and ionizing irradiation in murine L210 leukemia cells.	5 mg
PARP Inhibitor Set	**528820**	Contains 100 mg of 3-Aminobenzamide (Cat. No.165350), 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).	1 set
PARP Inhibitor XI, DR2313	**528819**	**{2-Methyl-3,5,7,8-tetrahydrothiopyrano[4,3-d]pyrimidine-4-one}** A brain-permeable and water soluble pyrimidinone compound that acts as a potent and NAD^+-competitive inhibitor of PARP (IC_{50} = 200 nM and 240 nM for rhPARP1 and rmPARP2, respectively) with little activity against the dehydrogenase activity of GAPDH, ADH, LDH, or the ADP-ribosylase activity of bacterial diphtheria toxin even at concentrations as high as 10 µM. Shown to inhibit H_2O_2-induced PAR formation and neuronal cell death in primary rat cerebral cortex culture *in vitro* (EC_{50} = 270 nM) and exhibit neuroprotective effects in both permanent and transient focal ischemia models in rat in *in vivo*.	5 mg
PARP Inhibitor XII	**528822**	**[3-(4-Chlorophenyl)quinoxaline-5-carboxamide]** A potent quinoxaline-based PARP inhibitor with a ~5-fold selectivity towards PARP-2 over PARP-1 (IC_{50} = 7 and 33 nM, respectively). Reported to be brain-permeant and exhibit good pharmacokinetics.	5 mg
PARP Inhibitor XIV	**528824**	**[BYK204165; 4-(1-Methyl-1H-pyrrol-2-ylmethylene)-4H-isoquinoline-1,3-dione]** A cell-permeable isoquinolinedione compound that potently inhibits PARP-1 activity (pIC_{50} = 7.35; IC_{50} = 45 nM) in a NAD^+-competitive and reversible manner, while affecting PPAR-2 activity with a 100-fold lower potency. Selectively inhibits PARP-1-mediated cellular PAR formation and is of little effect against PAR formation in fibroblasts derived from *parp-1(-/-)* mice. Its *in vivo* application is limited by a poor aqueous solubility (~9 µM).	10 mg
PJ34	**528150**	A cell-permeable, water-soluble phenanthridinone-derivative that acts as a potent inhibitor of poly(ADP-ribose) polymerase (PARP; EC_{50} = 20 nM). Shown to be about 10,000 times more potent than the prototypical PARP inhibitor, 3-Aminobenzamide (Cat. No.165350; EC_{50} = 200 µM). Does not act as an antioxidant at higher concentrations (1 µM to 10 mM). Exhibits neuroprotection in *in vivo* and *in vitro* models of stroke.	1 mg 5 mg

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

Product	Cat. No.	Comments	Size
TIQ-A	**612100**	**(4H-Thieno[2,3-c]isoquinolin-5-one)** A cell-permeable isoquinolinone compound that acts as a potent inhibitor of poly (ADP-ribose) polymerase-1 (IC_{50} = 450 nM for bovine recombinant PARP-1). Exhibits neuroprotective effects against ischemia both *in vitro* (IC_{50} = 150 nM in cultured murine cortical cells) and *in vivo* (3 mg/kg i.p. in a rat transient focal ischemia model). Reported to be ~20-fold more potent than DPQ (Cat. No.300270).	1 mg

Polyglutamine Aggregation Inhibitors

Product	Cat. No.	Comments	Size
Polyglutamine Aggregation Inhibitor III, C2-8	**528887**	**N-(4-Bromophenyl)-3-(((4-bromophenyl)amino)sulfonyl)benzamide** A cell-permeable amidosulfonamide compound that potently inhibits polyglutamine (polyQ)-aggregation in Huntington's disease (HD); CA1 neuronal hippocampal slices in the range of 0.1 µM - 10 µM, and Htt-103Q-EGFP PC12 cells with an IC_{50} of 50 nM. Further, relieves the progressive neurodegeneration in *Drosophila* expressing Httex1 93QP in a dose-dependent fashion. Suggested to block the polymerization step of the polyQ aggregation.	10 mg
Polyglutamine Aggregation Inhibitor, PGL-135	**528886**	**(2-Amino-4,7-dimethyl)benzothiazol-6-ol, HCl, (2-Amino-4,7-dimethyl-6-hydroxy)benzothiazole, HCl** A cell-permeable benzothiazole compound that binds to polyglutamine (polyQ)-containing ß-sheet structures and prevents polyQ-aggregation, a pathological hallmark of Huntington's disease (HD) and related glutamine repeat disorders. Shown to be non-toxic and prevent HDQ51 (FLAG®-tag HD exon 1 protein with 51 glutamines)-aggregation in 293 Tet-Off (293 tetracycline-off) cells with an IC_{50} of ~ 40 µM.	10 mg
Polyglutamine Aggregation Inhibitor, PGL-137	**528885**	**2-Dimethylamino-benzothiazol-6-ol, 2-Dimethylamino-6-hydroxybenzothiazole** A cell-permeable benzothiazole compound that binds to polyglutamine (polyQ)-containing ß-sheet structures and acts as a polyQ-aggregation inhibitor of Huntington's disease (HD). Shown to be non-toxic and prevent HDQ51 (flag-tagged HD exon 1 protein with 51 glutamines)-aggregation in 293 Tet-Off (293 tetracycline-off) cells with an IC_{50} of ~ 100 µM.	10 mg

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**	**[2-(*p*-Methoxybenzyl)-3,4-pyrrolidinediol-3-acetate]** Strongly activates stress-activated protein kinases (JNK/SAPK) and p38 MAP kinase in mammalian cells. Synergizes with growth factors to induce c-*fos* and c-*jun* by acting as a potent signaling agonist. An inhibitor of protein synthesis at the translation step. Also known to induce apoptosis in the human monoblastoid cell line, U937.	10 mg
Blasticidin S, Hydrochloride, *Streptomyces griseochromogenes*	**203350**	Nucleoside antibiotic that specifically inhibits protein synthesis in both prokaryotes and eukaryotes. Suitable for use as a dominant selectable marker in conjunction with blasticidin S resistant plasmids. Blasticidin S resistance is conferred by the blasticidin S deaminase gene (*bcr*), which converts blastisidin S to a nontoxic deaminohydroxy derivative.	25 mg
Chloramphenicol	**220551**	Synthetic bacteriostatic antibiotic that inhibits the translation of RNA by blocking the peptidyltransferase reaction on ribosomes.	25 g 100 g 500 g

Protein Synthesis Inhibitors *continued*

Product	Cat. No.	Comments	Size
Cycloheximide	**239763**	An antifungal antibiotic that inhibits protein synthesis in eukaryotes but not prokaryotes. Competitively inhibits hFKBP12 (K_i = 3.4 µM). Triggers apoptosis in HL-60 cells, T cell hybridomas, Burkitt's lymphoma cells, and other cell types. A 100 mg/ml solution of Cycloheximide (Cat. No.239765) in DMSO (sterile-filtered) is also available.	1 g 5 g
InSolution™Cycloheximide	**239765**	A 100 mg/ml DMSO solution (sterile-filtered) of cycloheximide (Cat. No. 239763) in DMSO.	1 ml
Cycloheximide, High Purity	**239764**	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. Competitively inhibits hFKBP12 (K_i = 3.4 µM). Triggers apoptosis in HL-60 cells, T cell hybridomas, Burkitt's lymphoma cells, and a variety of other cell types including rodent macrophages. However, it inhibits DNA cleavage in rat thymocytes treated with Thapsigargin (Cat. No.586005), methylprednisolone, and Ionomycin (Cat. Nos.407950 and407952). Rapidly destroyed in alkaline solutions.	100 mg 1 g
Emetine, Dihydrochloride	**324693**	**(6',7',10,11-Tetramethoxyemetan, 2HCl)** Principal alkaloid of ipecac, isolated from the ground roots of *Uragoga ipecacuanha*. Irreversibly blocks protein synthesis in eukaryotes by inhibiting the movement of ribosomes along the mRNA. Induces hypotension by blocking adrenoreceptors. Interferes with cytometric analysis of DNA replication at the early S phase.	250 mg
Erythromycin, *Streptomyces* erythreus	**329815**	**(Erythromycin A)** An antibacterial agent. Inhibits bacterial protein synthesis by binding to the 23S RNA in 50S ribosome.	5 g 25 g
G 418 Sulfate, Cell Culture Tested	**345810**	Aminoglycoside related to gentamycin that inhibits prokaryotic and eukaryotic protein synthesis. Toxic to bacteria, yeast, protozoans, helminths, higher plant, and mammalian cells. Widely used in the selection of eukaryotic expression vectors carrying the bacterial *neo*^{r}/*kan*^{r} genes. The product of these genes, aminoglycoside 3'-phosphotransferase, inactivates G418, neomycin, and kanamycin by phosphorylation. Introduction of either of these genes into cells can confer resistance to G418, which enables cells to grow in media containing G418.	250 mg 500 mg 1 g 5 g 25 g
G 418 Sulfate, Sterile-Filtered Aqueous Solution, Cell Culture Tested	**345812**	Sterile-filtered solution of Cat. No.345810 provided as 50 mg/ml active antibiotic.	10 ml 20 ml 50 ml
Hygromycin B, *Streptomyces sp.*	**400051**	Unique aminoglycoside antibiotic that inhibits the growth of prokaryotic (bacteria) and eukaryotic microorganisms (yeasts) and mammalian cells. Inhibits protein synthesis at the translocation step on the 70S ribosome and causes misreading of the mRNA. *Hph*, a gene from *E. coli*, encodes resistance to hygromycin B and can be isolated and cloned by recombinant DNA techniques. This hygromycin B-resistance gene is particularly useful for identification or selection of recombinant clones in a variety of cell types. Hygromycin B penetrates cells that have been permeabilized by virus infection and can act as an effective antiviral agent.	100 KU 1 MU 5 MU 10 MU
Kanamycin Sulfate, *Streptomyces kanamyceticus*	**420311**	**(Kamycin)** Contains more than 98% kanamycin A. An aminoglycoside antibiotic effective against Gram-positive and Gram-negative organisms. Inhibitor of protein biosynthesis that acts on the 30S ribosome, causing misreading of the genetic code. May cause renal damage and ototoxicity.	5 g 25 g
Kanamycin Sulfate, *Streptomyces kanamyceticus*, Cell Culture-Tested	**420411**	An aminoglycoside antibiotic effective against Gram-positive and Gram-negative organisms. Inhibitor of protein biosynthesis that acts on the 30S ribosome, causing misreading of the genetic code. May cause renal damage and ototoxicity.	5 g 25 g
Peptide Deformylase Inhibitor	**516500**	**[PDF2 Inhibitor; PDF1B Inhibitor; 2-(5-Bromo-1H-indol-3-yl)-N-hydroxyacetamide]** A cell-permeable hydroxamate compound that acts as an active site-binding, potent, and selective inhibitor against bacterial type peptide deformylases PDF2 and PDF1B (IC_{50} = 13 and 35 nM, respectively), while exhibiting little activity against human (mPDF) and *A. thaliana* (PDF1A) mitochondrial PDFs (IC_{50} = 360 and 130 µM, respectively). Shown to display similar antibiotic potency against *E. coli* and *B. subtilis* as, but less toxic towards human cells than, Actinonin.	10 mg
Protein Synthesis Initiation Inhibitor, NSC 119889	**539690**	**(3,4,5,6-Tetrabromofluorescein)** A cell-permeable, xanthenyl compound that prevents mRNA-ribosome interaction and inhibits 5'-mediated/cap-dependent initiation of protein synthesis (>95% inhibition at 50 µM in *in vitro* translation assays using Krebs, rabbit reticulocyte, or *E. coli* S30 extract).	25 mg
Puromycin, Dihydrochloride	**540222**	**[3'-(α-Amino-*p*-methoxyhydrocinnamamido)-3'-deoxy-N,N-dimethyladenosine, 2HCl]** Protein synthesis inhibitor. Inhibits translation by causing premature release of nascent polypeptide chains. Induces DNA fragmentation in thymocytes and in human HL-60 leukemia cells.	25 mg 100 mg

Protein Synthesis Inhibitors

Product	Cat. No.	Comments	Size
Puromycin, Dihydrochloride, Cell Culture-Tested	**540411**	Protein synthesis inhibitor. Inhibits translation by causing premature release of nascent polypeptide chains. Induces DNA fragmentation in thymocytes and in human HL-60 leukemia cells.	25 mg 100 mg
Siomycin A, *Streptomyces sioyaensis*	**567060**	**NSC 285116** A cell-permeable thiostrepton (Cat. No.598226) family macrocyclic peptide antibiotic that inhibits bacterial protein synthesis (IC_{50} = 250 nM) by interfering with rRNA binding. Shown to inhibit mammalian FoxM1 (forkhead box M1) function in C3 cells by negatively regulating its transcriptional activity (IC_{50} ≤5 µM), phosphorylation, as well as mRNA (>60% reduction at 10 µM) and protein (>90% reduction at 20 µM) abundance. Selectively induces apoptosis in SV40-transformed MRC-5 human fetal lung fibroblasts, but not the non-transformed wild-type cells.	500 µg
Spectinomycin, Dihydrochloride, Pentahydrate, *Streptomyces* sp.	**567570**	A broad spectrum aminoglycoside antibiotic that contains two glucose moieties. Footprint studies indicate that spectinomycin exerts regional effects on ribosomal structure. A resistance gene (*aph*) which encodes a spectinomycin has been cloned from *Legionella pneumophila* (disease agent for Legionnaire's disease) kinase and expressed in *E. coli*. *Potency:* ≥500 µg/mg.	10 g
Streptomycin Sulfate, *Streptomyces* sp.	**5711**	Antibiotic effective against Gram-positive and Gram-negative bacteria. Often used in culture media to control growth of microorganisms. Inhibits initiation, elongation, and termination of protein synthesis in prokaryotes and induces misreading of the genetic code.	100 g
Tetracycline, Hydrochloride	**58346**	Broad-based antibiotic agent that blocks protein synthesis by inhibiting binding of aminoacyl tRNA to the A-site of ribosomes. Induces cold shock-response and enhances P450 expression in bacteria.	10 g 25 g 50 g
Tetracycline, Hydrochloride, Cell Culture-Tested	**583411**	Broad-based antibiotic agent that blocks protein synthesis by inhibiting binding of aminoacyl tRNA to the A-site of ribosomes. Induces cold shock-response and enhances P450 expression in bacteria.	10 g 25 g
Thiostrepton	**598226**	A thiazole-containing peptide antibiotic that inhibits protein synthesis by preventing binding of GTP to 50S ribosomal subunit. Inhibits the function of elongation factor G (EF-G) and the dissociation of EF-G from the ribosome. The thiostrepton-resistant gene is also commonly used as a selective marker for recombinant DNA/plasmid technologies.	1 g 10 g
Tobramycin, Free Base	**614005**	Aminoglycoside antibiotic active against Gram negative bacteria. Inhibits myeloperoxidase-dependent oxidant cell injury.	100 mg

RNA-editing Ligase Inhibitors

Product	Cat. No.	Comments	Size
RNA-Editing Ligase 1 Inhibitor, NSC 45208	**557401**	**4,5-Dihydroxy-3-(1-naphthyldiazenyl)-2,7-naphthalenedisulfonic acid, disodium salt, dihydrate** A sulfonated azo dye, initially identified by a *Trypanosoma burcei* RNA-editing ligase 1 (*Tb*REL1) crystal structure-based inhibitor screening, is shown to inhibit *Tb*REL1 activity (IC_{50} = 1.95 µM) by targeting the enzyme's ATP binding pocket. V1 is less potent against T4 phage RNA ligase 2 and human DNA ligase IIIß (IC_{50} = 3.53 and 27.49 µM, respectively).	50 mg

Translational Initiation Inhibitors

Product	Cat. No.	Comments	Size
eIF-2α Inhibitor II, Sal003	**324896**	**3-Phenyl-N-(2,2,2-trichloro-1-((((4-chlorophenyl) amino)carbonothioyl)amino)ethyl)acrylamide** A cell-permeable Salubrinal (Cat. No.324895) analog that is reported to be more potent and soluble than Salubrinal. In addition to being a useful tool in studying eIF2α-mediated cellular processes in cultures *in vitro*, enhanced eIF2α phosphorylation by Sal003 treatment in the brain (40 pmol per animal) is shown to impair long-term memory in mice *in vivo*.	5 mg
eIF4E/eIF4G Interaction Inhibitor, 4EGI-1	**324517**	**2-((4-(3,4-Dichlorophenyl)-thiazol-2-ylhydrazono)-3-(2-nitrophenyl))propionic acid** A cell-permeable hydrazone compound that reversibly binds eukaryotic translation initiation factor 4E (eIF4E; K_D = 25 µM) and disrupts eIF4E/eIF4G, but not eIF4E/4E-BP1, complex formation. Reported to downregulate the protein, but not mRNA, levels of c-Myc and Bcl-x_L in Jurkat cells (8 h), leading to apoptotic cell death after prolonged exposure (24 h, IC_{50} = ~ 25 µM).	10 mg

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TNF-α Inhibitors

Product	Cat. No.	Comments	Size
TNF-α Antagonist	**654255**	**TNF-α Antagonist, Tumor Necrosis Factor-α Antagonist** An exocyclic peptidomimetic that acts as a TNF-α antagonist (IC_{50} = 5 µM) in the binding assay. Blocks TNF-α-mediated apoptosis in mouse L929 cells. The designation WP9QY arises from the binding to the site observed in the TNF-ß/TNF-receptor (I) complex as template, and the introduction of amino acids Glu and Tyr.	1 mg
TNF-α Antagonist III, R-7050	**654257**	**8-Chloro-4-(phenylsulfanyl)-1-(trifluoromethyl)[1,2,4]triazolo[4,3-a]quinoxaline** A cell-permeable triazoloquinoxaline compound that acts as a TNF-α receptor antagonist via the blockage of receptor-adaptor molecules complex formation and subsequent receptor internalization, but not TNF-α ligand-receptor binding. Shown to selectively inhibit TNF-α-, but not Fas- or C6-ceramide-, induced caspase activation and cell death in ME180 cells and exhibit higher potency against TNF-α-induced than IL-1ß-induced NF-κB activation (EC_{50} = 0.631 and 1.45 µM, respectively) in A549 cells.	10 mg
TNF-α Inhibitor	**654256**	**6,7-Dimethyl-3-((methyl-(2-(methyl-(1-(3-trifluoromethyl-phenyl)-1H-indol-3-ylmethyl)-amino)-ethyl)-amino)-methyl)-chromen-4-one, diHCl, TNF-α Inhibitor, Tumor Necrosis Factor-α Inhibitor** A cell-permeable indolyl-chromenone compound that rapidly inactivates TNF-α by non-covalently binding to the TNF-α trimer and promoting subunit dissociation and preventing TNF-α binding to its receptor (IC_{50} = 22 µM). Shown to selectively inhibit TNF-α-, but not IL-1ß-induced IκB-α degradation in HeLa cells (IC_{50} = 4.6 µM).	5 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, and others. We recommend surveying the literature to determine the initial concentration. If published K_i or IC_{50} values are known, use 5–10 times higher inhibitor amounts than these values to maximally inhibit enzyme activity. If K_i or IC_{50} values are unknown, then 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. 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, pIC_{50}?

In pharmacology and biochemistry, the following terms are commonly used to determine the efficacy of a drug or inhibitor. 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, pIC_{50} dissociation of an inhibitor or substrate from an enzyme.

pIC_{50}: The negative logarithm to base 10 of the IC_{50}.

How much inhibitor or stimulator should be injected into an animal?

There is no simple answer to this question. 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. 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 240-480 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 µg/liter. Because the volume of distribution is about 140 ml, 124.63 × 0.140 = 17.45 µg 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 an inhibitor?

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, 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.

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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, Cat. No. 371963, or 8-Br-cAMP, Rp isomer, Cat. No. 116816), PKC (e.g., Bisindolylmaleimide, Cat. No. 203290), or PKG (e.g., KT5823, Cat. No. 420321; or PKG inhibitor, Cat. No. 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 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. Additionally, it is important to avoid EDTA when preparing extracts for IMAC (e.g., His•Tag® purification). If you are not sure of the type of proteases present in the sample, it is best to use or customize your own cocktails.

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San Diego

Our San Diego, CA facility has taken many steps, small and large, to propagate environmental responsibility. 60,000 pounds of hazardous waste have been diverted from disposal in a landfill to being recycled and used as power by a partner company in cement kilns. Instead of disposing obsolete inventory as hazardous waste, we donate over 4000 chemicals to local start-up companies. The latest site improvement is the installation of heat pump economizers that circulate fresh air into the building when the outside temperature is below set point which has reduced energy consumption by 30%.

Stewardship is part of who we are...

not because we must, but because

it's the right thing to do.

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