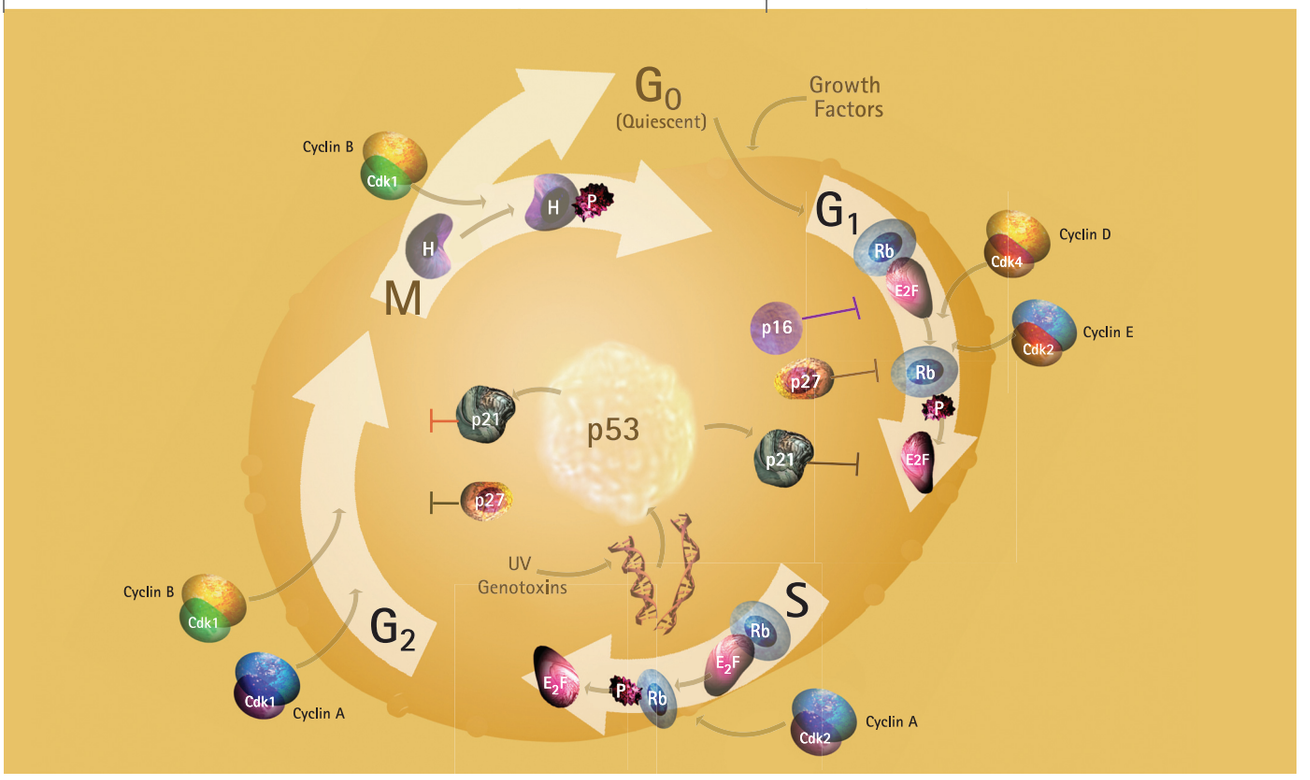
Molecular Targets for Cancer Chemotherapy

The enzymatic activity of cyclin-dependent kinases (Cdks) is regulated at three levels: cyclin association, subunit phosphorylation, and association with Cdk inhibitors (CKIs). Two main categories of CKIs reported in cells include the INK and WAF/Kip families. The members of the INK family, $p15^{Ink4b}$, $p16^{Ink4a}$, $p18^{Ink4c}$, and $p19^{Ink4d}$ inhibit the activities of Cdk4 and Cdk6 by binding and blocking their interaction with D-type cyclins. The members of the WAF/KIP family, $p21^{Waf1,}$ $p27^{Kip1}$, and $p57^{Kip2}$, form heterotrimeric complexes with the G_1/S Cdks. Their major action is reported to be the inhibition of the kinase activity of the Cdk/cyclin-E complex. p21 also binds to the DNA polymerase δ processivity factor, proliferating-cell nuclear antigen (PCNA), and inhibits PCNA-dependent DNA replication. The Cdk and PCNA inhibitory activities of p21 are shown to be functionally independent and reside in separate protein domains. The PCNA binding and inhibitory activities that are not observed with p27 or p57, reside in the C-terminal domain of p21, whereas the Cdk inhibitory activity resides in the conserved N-terminal domains of these proteins. It is important to note that binding between most CKIs and Cdks display some degree of specificity, however, p21 has been shown to be a universal Cdk inhibitor and is the only CKI whose promoter is activated by p53, thereby providing a rational model linking tumor suppression by p53 with cell cycle regulation.

Members of the retinoblastoma protein family, Rb, p107, and p130, serve as the primary substrates of Cdk4/6 and Cdk2 in G_1 progression. They act as 'docking' sites for a number of proteins involved in the cell cycle. For example, Rb proteins bind to the E2F transcription factors and guarantee their inactive state during M and G_0 phases. The Rb–E2F complex also participates in the active repression of selected promoters of cell cycle. The activity of the Rb proteins is modulated by sequential phosphorylation by Cdk4/6-cyclin D and Cdk2/cyclin E complexes. Rb proteins are also regulated by histone acetylase- mediated acetylation, which prevents the phosphorylation of Rb protein by Cdk2/cyclin E.

Cell-cycle regulators are frequently mutated in human cancers, which may lead to over-expression of cyclins and Cdks, as well as loss of Rb and CKI activity, mainly $p15^{Ink4b}$, $p16^{Ink4a}$, and $p27^{Kip1}$. Cancer cells often show abnormalities in the signal transduction pathways that lead to proliferation in response to external signals. Indeed, many growth factor receptors and their downstream effectors have been identified as oncogenes or tumor-suppressor genes.

Currently, much optimism exists regarding the possibility of finding new anti-cancer drugs that can modulate cell cycle regulatory molecules. From a therapeutic standpoint Cdks are considered to be the most promising targets in cancer chemotherapy. Most of the currently available molecules target the ATP-binding site of the enzymes. Such an approach creates problems as residues at catalytic sites are well conserved across eukaryotic protein kinases. However, compounds such as flavopiridol, olomucine, and butyrolactone-1 that exhibit greater specificity for Cdks have shown some promise in clinical trials.



NEW! Potent Cdk Inhibitor

SU9516 [3-(1-(3H-Imidazol-4-yl)-meth-(Z)-ylidene]-5-methoxy-1,3-dihydro-indol-2-one]

A cell-permeable, potent, selective, 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). Does not significantly affect the activities of PKC, p38, PDGFRβ, or EGFR (IC_{50} > 10 µM). *Purity: ≥95% by HPLC.*

Cat. No. 572650 **5 mg** **$ 95**

Ref.: Yu, B., et al. 2002. *Biochem. Pharmacol.* **64,** 1091; Lane, M.E., et al. 2001. *Cancer Res.* **61,** 6170.

Also Available...

Cdk5, GST-Fusion, Human, Recomb., *E. coli*

Cdk5 together with p35 or p39 forms an active enzyme complex, which phosphorylates a variety of substrates involved in various cellular functions. Aberrant Cdk5 activity has been implicated in several disease conditions.

Cat. No. 219459 **250 Units** **$ 252**

Ref.: Lee, K.Y., et al. 1999. *Neurosci. Res.* **34,** 21; Lee, K.Y., et al. 1997. *J. Biol. Chem.* **272,** 5622; Lee, K.Y., et al. 1996. *J. Biol. Chem.* **271,** 1538; Tang, D., et al. 1995. *J. Biol. Chem.* **270,** 26897.

Chk1, His•Tag®, Human, Recombinant

The full length Chk1 expressed in insect cells. Chk1 is a Serine/Threonine kinase that regulates cell cycle progression. DNA damage causes an increase in activity and phosphorylation of Chk1. *Purity: ≥90% by SDS-PAGE.*

Cat. No. 220479 **10 µg** **$ 315**

Ref.: Heffernan, T.P., et al. 2002. *Mol. Cell. Biol.* **22,** 8552; Zhao, H., and Piwnica-Worms, H. 2001. *Mol. Cell. Biol.* **21,** 4129; Hutchins, J.R., et al. 2000. *FEBS Lett.* **466,** 91.

Retinoblastoma Protein, Human, Wild Type, Recombinant

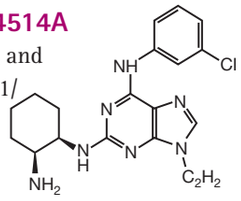
A product of retinoblastoma susceptibility gene *Rb-1*. Mutations in *Rb-1* gene leads to development of various tumors. The activity of pRb is regulated through phosphorylation in a cell cycle-dependent manner. The hyperphosphorylated Rb protein usually associates with the cell nucleus and binds transcription factors of the E2F family. pRb also represses transcription of its target genes through the binding with E2F factors. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 554706 **5000 Units** **$ 475**

Ref.: Trimarchi, J.M., and Lees, J.A. 2002. *Nat. Rev. Mol. Cell. Biol.* **3,** 11; Dyson, N. 1998. *Genes Dev.* **12,** 2245; Onadim, Z., et al. 1992. *Proc. Natl. Acad. Sci. USA* **89,** 6177; Hinds, P.W., et al. 1992. *Cell* **70,** 993.

NEW! Cyclin-Dependent Kinase Inhibitors

CDK1 Inhibitor, CGP74514A



A cell-permeable, potent, and selective inhibitor of Cdk1/cyclin B (IC_{50} = 25 nM) that affects other kinases only at significantly higher concentrations (IC_{50} = 6.1 µM, 125 µM, and >10 µM for PKC-α, PKA, and EGFR, respectively). Shown to induce mitochondrial damage and apoptosis (≥ 3 µM) in several human leukemia cell lines. *Purity: ≥95% by HPLC.*

Cat. No. 217696 5 mg $ 120

Ref.: Yu. C., et al. 2003. *Cancer Res.* **63,** 1822; Dai, Y., et al. 2002. *Cell Cycle* **1,** 143; Imbach, P., et al. 1999. *Bioorg. Med. Chem. Lett.* **9,** 91. Sold under license from Novartis Pharma AG.

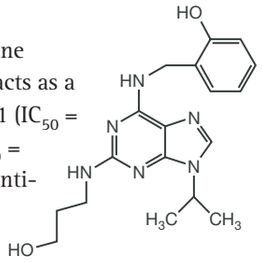
Cdk1 Inhibitor III [Ethyl-(6-hydroxy-4-phenyl-benzo[4,5]furo-[2,3-b]) pyridine-3-carboxylate]

A cell-permeable, selective inhibitor of Cdk1/B (IC_{50} = 28.8 µM) that exhibits P-glycoprotein modulating properties. *Purity: ≥97% by HPLC.*

Cat. No. 217697 1 mg $ 80
5 mg $ 290

Ref.: Brachwitz, K., et al. 2003. *J. Med. Chem.* **46,** 876.

Cdk Inhibitor, p35

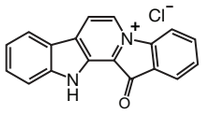


An analog of Olomoucine (Cat. No. 495620) that acts as a potent inhibitor of Cdk1 (IC_{50} = 100 nM) and Cdk2 (IC_{50} = 80 nM). Also displays anti-proliferative and pro-apoptotic effects. *Purity: ≥95% by HPLC.*

Cat. No. 219457 1 mg $ 67

Ref.: Vermeulen, K., et al. 2002. *Leukemia* **16,** 299.

Fascaplysin, Synthetic



A cell-permeable, potent ATP-competitive inhibitor of Cdk4/D1 (IC_{50} = 350 nM). It inhibits Cdk6/D1 with much lower potency (IC_{50} = 3.4 µM). Does not affect the activities of several other Cdk's (IC_{50} > 20 µM) and tyrosine kinases (IC_{50} > 10 µM). *Purity: ≥98% by NMR.*

Cat. No. 341251 1 mg $ 75

Ref.: Hormann, A., et al. 2001. *Bioorg. Med. Chem.* **9,** 917; Kirsch, G., et al. 2000. *J. Nat. Prod.* **63,** 825; Soni, R., et al. 2000. *Biochem. Biophys. Res. Commun.* **275,** 877.

Interested in SARS-Related Research? Introducing...

Coronavirus Main Proteinase Inhibitor (Cbz-VNSTLQ-CMK)

An irrversible substrate-analog inhibitor of several viral proteinases that covalently modifies the active site cysteine residue. The peptide is derived from the P6 - P1 residues of the NH_2-terminal autoprocessing site of porcine TGEV M^{pro} (transmissible gastroenteritis virus main proteinase) and is expected to bind to all other coronavirus homologs, such as human SARS-CoV M^{pro} and HCoV 229E M^{pro}, in a similar manner and with similar affinity. *Purity: ≥95% by HPLC.*

Cat. No. 235035 1 mg $ 95
5 mg $ 360

Ref.: Anand, K., et al. 2003. *Science* **300,** 1763.

Glycyrrhizin, Ammonium Salt

A triterpenoid saponin with antiviral and anti-tumor activities. Inhibits replication, adsorption, and penetration of severe acute respiratory syndrome-associated coronavirus (SARS-CV), presumably via its ability to upregulate nitric oxide synthase activity. *Purity: ≥98% by HPLC.*

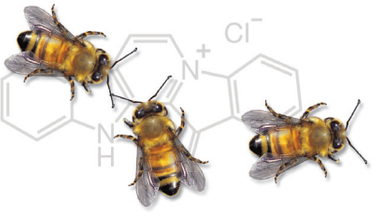
Cat. No. 356780 5 g $ 50

Ref.: Cinatl, J., et al. 2003. *Lancet* **361,** 2045; Kondo, Y., and Takano, F. 1994. *Biol. Pharm. Bull.* **17,** 759.

NEW! Antibodies for Cell Cycle Research

Product	Cat No.	Comments and Applications*	Size	US $
Anti-14-3-3β, Rat (Mouse)	AP1000**	Detects the ~31 kDa 14-3-3β, a member of the 14-3-3 family of proteins which have been implicated in several cellular processes including cell proliferation, cell cycle progression, differentiation, and apoptosis. **IB, IP**	100 µg	295
Anti-14-3-3β/ε/ζ, Human (Mouse)	AP1001**	Detects the ~30 kDa β, ε, and ζ isoforms of 14-3-3. 14-3-3ζ has been reported to be a substrate for Akt. **IB**	100 µg	295
Anti-Cdc25A, Human (Rabbit)	PC733	Detects the ~67 kDa Cdc25A, a labile phosphatase required for DNA replication via the activation of Cdk2. **IB, IP**	100 µl	275
Anti-E2F4 (Ab-2), Human (Mouse)	NA78	E2F4 is a ~60 kDa transcription factor. When hyperphosphorylated or complexed with p130, it is a putative marker of cellular quiescence. **IB**	100 µl	295
Anti-E2F6, Human (Mouse)	NA79	E2F6 is a ~38 kDa transcription factor. Lacks the sequences responsible for both transactivation and binding to the retinoblastoma protein. Can act as a dominant negative inhibitor of other E2F family members. **IB**	100 µl	304
Anti-Pescadillo 1, Mouse (Rabbit)	DR1011	Detects the ~68 kDa pescadillo, a nuclear cell cycle regulatory protein which has been reported to be abnormally expressed in malignant astrocytes and other transformed cell lines. **IB, IC**	100 µl	295
Anti-Pumilio 1, Human (Goat)	DR1012	Detects the ~127 kDa pumilio, an RNA binding protein which may play a role in the regulation of self-renewal of mammalian stem cells. **IB, IP**	100 µl	295
Anti-Rb, Phospho-Specific (Ser^{612}), Human (Rabbit)	CA1006	Detects the ~105 kDa Rb protein phosphorylated on Ser^{612}. Ser^{612} phosphorylation is catalyzed by Cdk2 complexes such as Cyclin E-Cdk2 and Cyclin A-Cdk2. **IB**	10 T	315
Anti-Rb, Phospho-Specific (Ser^{780}), Human (Rabbit)	CA1007	Detects the ~105 kDa Rb protein phosphorylated on Ser^{780}. Ser^{780} phosphorylation is catalyzed by Cdk2 complexes. This phosphorylation has been reported to disrupt binding to E2F. **IB**	10 T	315
Anti-Rb, Phospho-Specific (Ser^{807}), Human (Rabbit)	CA1008	Detects the ~105 kDa Rb protein phosphorylated on Ser^{807}. Ser^{807} phosphorylation is catalyzed by Cdk2 complexes such as Cdk4-D1. This phosphorylation has been reported to disrupt binding to E2F. **IB**	10 T	315
Anti-Rb, Phospho-Specific (Ser^{811}), Human (Rabbit)	CA1009	Detects the ~105 kDa Rb protein phosphorylated on Ser^{811}. Ser^{811} phosphorylation is catalyzed by Cdk2 complexes such as Cdk4-D1. This phosphorylation has been reported to disrupt binding to E2F. **IB**	10 T	315

***Key: IB:** Immunoblotting; **IC:** Immunocytochemistry; **IP:** Immunoprecipitation; **Note:** 1 T = 1 Test; ** Not available for sale in Japan

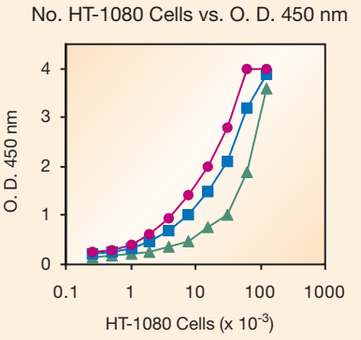


Introducing... New Kits for Cell Proliferation Assay

Rapid Cell Proliferation Kit

Assay based on the increased activity of cellular mitochondrial dehydrogenases that can cleave the tetrazolium dye WST-1 to formazan. The formazan dye formation is then quantified by measuring the change in absorbance at 450 nm in a microplate reader. The activity of mitochondrial dehydrogenases is proportional to cell number. Kit does not involve any washing, harvesting, or solubilization steps. Each kit is suitable for up to 500 assays and includes WST-1, 1-Methoxy PMS, and a directional insert.

Cat. No. QIA127 1 Kit $ 175

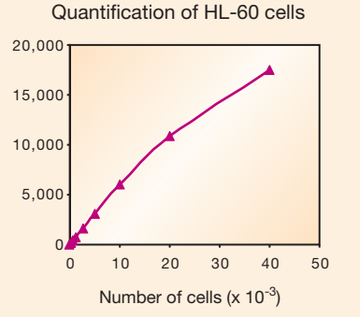


HT-1080 cells incubated for 20 hours followed by the addition of WST-1 labeling mixture. After additional 1 (▲), 2.5 (■), and 4 hour (●) incubations, the absorbance was read at 450 nm.

Ultrasensitive Cell Proliferation Reagent Set, Fluorogenic

A highly sensitive cell proliferation assay utilizing Calcein-AM, a fluorescent probe for staining viable cells (excitation max.: ~485 nm; emission max.: ~520 nm). For optimal results serum-free media or Dulbecco's PBS is recommended. Extremely useful for cytotoxicity assays. Each kit is suitable for up to 500 tests.

Cat. No. QIA128 1 Kit $ 165



Quantification of HL-60 cells using the Ultrasensitive Cell Proliferation Reagent Set. Fluorescence was measured in a microplate reader with excitation at 485 nm and emission at 520 nm. Cells were incubated with the Calcein-AM working solution for 1 hour at 37˚C in a CO_2 incubator.

Looking for Topoisomerase?

Topoisomerase I, Human, Mutant Y723F, Recombinant

The mutant Y723F of DNA topoisomerase I. Mutation from tyrosine to phenylalanine at position 723 results in preferential binding of the topoisomerase to supercoiled DNA rather than relaxed DNA in a mixture of supercoiled and relaxed DNAs. However, this mutation affects neither the topoisomerase's kinase activity nor the transcription activity of class II genes *in vitro*. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 614851 5000 Units $ 395

Ref.: Rossi, F., et al. 1998. *Nucleic Acids Res.* **26,** 2963; Wang, Z., et al. 1998. *Mol. Cell* **1,** 749; Madden, K.R., et al. 1995. *EMBO J.* **14,** 5399.

Topoisomerase I, Human, Wild Type, Recombinant

Human DNA topoisomerase I catalyzes the relaxation of both positive and negative supercoiled DNAs without any energy requirement. Also plays a major role in pre-mRNA splicing, cell cycle and other gene regulatory pathways during cell growth and development. Activity: 1.0 unit/ng of purified protein. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 614850 5000 Units $ 395

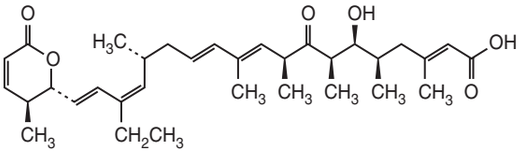
Ref.: Pommier, Y., et al. 1998. *Biochim. Biophys. Acta* **1400,** 83; Pourquier, P., et al. 1997. *J. Biol. Chem.* **272,** 26441; Sekiguchi, J., et al. 1996. *Proc. Natl. Acad. Sci. USA* **93,** 785; Rossi, F., et al. 1996. *Nature* **381,** 80.

Interested in Nuclear Export Blockers? Check Out Our Low Prices!

Leptomycin B, *Streptomyces* sp.

Leptomycin B, an unsaturated, branched-chain fatty acid with a terminal lactone ring that acts as a potent inhibitor of Crm1 (exportin-1)-mediated nuclear export. Exhibits antibiotic, antifungal, and antitumor properties and blocks the progression of the cell cycle at G_1 and G_2 phases. Protects p53 from Mdm2-mediated degradation and induces p53 transcriptional activity. Also reported to inhibit the nucleo-cytoplasmic translocation of the human immunodeficiency virus type 1 regulatory protein *Purity: ≥95% by HPLC.*

Cat. No. 431050 **1 µg** **$ 295**



Ref.: Menéndez, S. et al. 2003. *Br. J. Cancer* **88,** 636; Kudo N, et al. 1999. *Proc. Natl. Acad. Sci. USA* **96,** 9112; Kuhnt, M., et al. 1998. *Appl. Environ. Microbiol.* **64,** 714; Wolff, B. et al. 1997. *Chem. Biol.* **4,** 139; Yoshida, M. et al. 1990. *Exp. Cell Res.* **187,** 150; Komiyama, K. et al. 1985. *J. Antibiot.* **38,** 427.

Leptomycin A, *Streptomyces* sp.

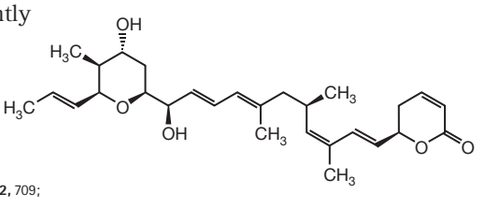
An antifungal antibiotic that acts as an inhibitor of nuclear export. Shown to inhibit nucleo-cytoplasmic translocation of Rev at nanomolar concentrations. *Purity: ≥95% by HPLC.*

Cat. No. 431051 **1 µg** **$ 145**

Ref.: Hamamoto, T., et al. 1985. *J. Antibiot.* **38,** 533; Hamamoto, T., et al. 1983. *J. Antibiot.* **36,** 646; Hamamoto, T., et al. 1983. *J. Antibiot.* **36,** 639.

Ratjadone A, Synthetic

A cell-permeable polyketide antitumor agent that inhibits nuclear export of LR-NES (leucine rich-nuclear export signal)-containing proteins by covalently binding to CRM1. Inhibits cell proliferation (IC_{50} = 1 ng/ml) and induces cell cycle arrest at G_1 phase. *Purity: ≥95% by HPLC.*



Cat. No. 553590 **2 µg** **$ 185**

Ref.: Koster, M., et al. 2003. *Exp. Cell Res.* **286,** 321; Kalesse. M., et al. 2001. *Chembiochem* **2,** 709; Gerth, K., et al. 1995. *J. Antibiotics* **48,** 973.

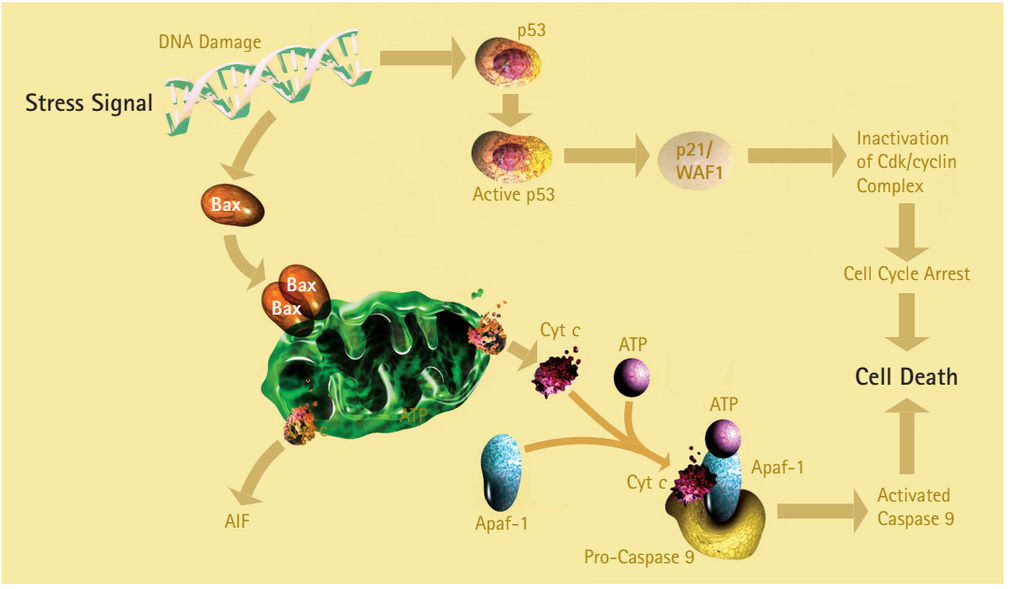
NEW! Antibodies for Structural Maintenance of Chromosomes (SMC) Proteins

Product	Cat No.	Comments and Applications*	Size	US $
Anti-SMC1, Human (Rabbit)	PC737	Detects the ~160 kDa SMC1 which is a chromosomal protein necessary for sister chromatid cohesion and may be involved in DNA repair. **IB, IF, IP**	100 µl	275
Anti-SMC1, Phospho-Specific (Ser^{957}), Human (Rabbit)	PC738	Detects the ~160 kDa SMC1 phosphorylated on Ser^{957}. Does not detect the unphosphorylated protein. **IB, IP**	100 µl	325
Anti-SMC1, Phospho-Specific (Ser^{966}), Human (Rabbit)	PC739	Detects the ~160 kDa SMC1 phosphorylated on Ser^{966}. Does not detect the unphosphorylated protein. **IB, IP**	100 µl	325
Anti-SMC3, Human (Rabbit)	PC740	Detects the ~140 kDa SMC3. SMC3 has been reported to be over-expressed in human colon carcinoma. **IB, IF, IP**	100 µl	275
Anti-SMC3, Phospho-Specific (Ser^{383}), Human (Rabbit)	PC741	Detects the ~140 kDa SMC3 phosphorylated on Ser^{383}. SMC3 is phosphorylated on Ser^{383} in response to ionizing radiation. **IP**	100 µl	325

Key: IB: Immunoblotting; **IF:** Immunofluorescence; **IP:** Immunoprecipitation

Bax-induced Apoptosis: Death by Mitochondrial Pores

Bax, a pro-apoptotic protein of the Bcl-2 family, is normally found in the cytosol and acts as a sensor of cellular damage and stress. In response to significant damage or stress it relocates to the mitochondrial surface and disrupts the normal function of the anti-apoptotic Bcl-2 proteins. Normally Bax resides in the cytosol as a monomer. However, in cells undergoing apoptosis, Bax associated with the mitochondria can be present as an inactive monomer or as an active large molecular weight complex integrated into the mitochondrial membrane. Bax can form transmembrane pores across the outer mitochondrial membrane, which leads to loss of membrane potential and efflux of cytochrome c (Cyt *c*) and the apoptosis inducing factor (AIF). Cyt *c* together with Apaf-1 and ATP forms a complex with pro-caspase 9 (apoptosome), leading to activation of caspase 9. Binding to Cyt *c* makes Apaf-1 more competent at binding pro-caspase-9. The N-terminus of Apaf-1 has the caspase recruitment domain (CARD), which is shared by caspases 1, 2, 3, 4, and 9. Since Apaf-1 does not have any caspase activity, pro-caspase-9 is believed to be activated through autocatalysis in the apoptosome. In this scheme of events anti-apoptotic molecules, Bcl-2 and Bcl-x_L, act to prevent mitochondrial pore formation. When Bax heterodimerizes with Bcl-2 or Bcl-x_L, it blocks their anti-apoptotic effects.



Bax-Inhibiting Peptide, V5 (H-VPMLK-OH)

A cell-permeable peptide based on the Ku70-Bax inhibiting domain that offers cytoprotection against Bax-mediated apoptosis (~ 50 - 200 µM). Effectively blocks caspase-independent necrotic cell death. Shown to interact with Bax and prevent its conformational change and mitochondrial translocation. *Purity: ≥95% by HPLC.*

Cat. No. 196810 **5 mg** **$ 80**

Ref.: Sawada, M., et al. 2003. *Nat. Cell Biol.* **5,** 352.

Bax-Inhibiting Peptide, Negative Control (H-IPMIK-OH)

A cell-permeable mutated analog of the Bax-Inhibiting Peptide, V5 (Cat. No. 196810) that can be used as a negative control. *Purity: ≥97% by HPLC.*

Cat. No. 196811 **5 mg** **$ 80**

Ref.: Sawada, M., et al. 2003. *Nat. Cell Biol.* **5,** 352.

Bcl-x_L Assay Substrate, Fluorogenic (Ac-NLWAAQRYGRELRRMSDK(fluorescein)FVD-OH)

A fluorescein-labeled Bad BH3 peptide that serves as a probe for investigating the nature of Bcl-x_L-peptide interaction and as a substrate for high-throughput screening of Bcl-x_L inhibitors based on fluorescence polarization. Interacts strongly with Bcl-x_L (K_d = 21.48 nM). The assay tolerates up to 8% DMSO. *Purity: ≥95% by HPLC.*

Cat. No. 197216 1 mg $ 275

Ref.: Zhang, H., et al. 2002. *Anal. Biochem.* **307,** 70.

Humanin, Human, Synthetic (H-MAPRGFSCLLLLTSEIDLPVKRRA-OH)

A 24-residue anti-apoptotic peptide that offers protection against neuronal apotosis induced by presenilin and amyloid precursor protein mutants associated with familial Alzheimer's disease (AD). Reduces cytochrome *c* release by directly binding to Bax (K_d ~ 2 nM) and preventing its association with isolated mitochondria. *Purity: ≥95% by HPLC.*

Cat. No. 400140 1 mg $ 240

Ref.: Guo, B., et al. 2003. *Nature* **423,** 456; Hashimoto, Y., et al. 2003. *J. Neurochem.* **84,** 864; Hashimoto, Y., et al. 2001. *J. Neurosci.* **21,** 9235.

NEW! Antibodies for Apoptosis Research

Product	Cat No.	Comments and Applications*	Size	US $
Anti-Cleaved α-Fodrin (Asp[1185]), Human (Rabbit)	AP1011	Immunogen used was a synthetic peptide corresponding to N-terminal residues adjacent to Asp[1185] of α-fodrin. Detects the ~150 kDa α-fodrin protein cleaved at Asp[1185] by caspases. Does not recognize the full-length, 240 kDa α-fodrin. **IB, IC**	50 µl	195
Anti-Fos, Phospho-Specific (Ser[374]), Human (Mouse)	ST1029	Detects the ~55 kDa c-Fos, which is phosphorylated on Ser[374] by MAP kinase. Does not detect the unphosphorylated form. **IB**	100 µg	315
Anti-Cleaved Interleukin-1β (Asp[116]), Human (Rabbit)	AP1016	Immunogen used was a synthetic peptide corresponding to amino acid residues from the N-terminal sequence of the mature form of IL-1β. Detects the ~17 kDa IL-1β, which is cleaved from the 31 kDa precursor by caspase-1. Does not detect the precursor from of IL-1β. **IB**	50 µl	195
Anti-Cleaved Lamin A (Asp[230]), Human (Rabbit)	AP1017	Immunogen used was a synthetic peptide corresponding to C-terminal amino acid residues adjacent to Asp[230] of lamin A. Detects the ~45-50 kDa large subunit of lamins A and C. Does not recognize full length lamin A. **IB, IC, PS**	50 µl	195
Anti-Livin, Human (Goat)	PC724	Immunogen used was a synthetic peptide corresponding to amino acid residues 267-277 of livin. Detects the ~30 kDa livin, an inhibitor of apoptosis protein (IAP) capable of inhibiting DEVD-like caspase activity. **IB**	100 µg	295
Anti-NRAGE, Rat (Rabbit)	AP1006	Immunogen used was a GST-fusion protein containing amino acids 53-295 of NRAGE. Detects the ~85 kDa NRAGE that induces neuronal apoptosis by activating the mitochondrial apoptotic cascade. Reacts with human, mouse, and rat. **IB, IC, IP**	100 µl	226
Anti-TRADD, Human (Mouse)	AP1005	Immunogen used was a full length, recombinant human TRADD. Detects the ~34 kDa TRADD, an adaptor protein associated with the TNF receptor-1 complex. **IB**	100 µg	295
Anti-TRAF1, Mouse (Mouse)	AP1002**	Immunogen used was full length, recombinant TRAF1. Detects the ~56 kDa TRAF1. **IB**	100 µg	295
Anti-TRAF2, Mouse (Rabbit)	AP1003**	Immunogen used was full-length, recombinant TRAF2 GST-fusion protein. Detects the 58 kDa human and 56 kDa mouse TRAF2. **IB**	100 µg	295
Anti-TRAF6, Mouse (Rabbit)	AP1004**	Immunogen used was a recombinant TRAF6 GST-fusion protein containing amino acids 1-305. Detects the 58 kDa TRAF6. **IB, IP**	100 µg	295

Key: IB:** Immunoblotting; **IC:** Immunocytochemistry: **IP:** Immunoprecipitation: **PS:** Paraffin Sections; *:** Not available for sale in Japan

NEW! Protein Kinase Inhibitors

AGL 2043

A cell-permeable, potent, selective, ATP-competitive, and reversible inhibitor of type III receptor tyrosine kinases PDGFR (IC_{50} = 800 nM in 3T3 cells; 90 nM against purified PDGFβ-receptor), Flt3, and Kit (IC_{50} = 1-3 µM). *Purity: ≥95% by HPLC.*

Cat. No. 121790 1 mg $ 175

Ref.: Gazit, A., et al. 2003. *Bioorg. Med. Chem.* **11,** 2007.

AG 957, Adamantyl Ester

A lipophilic, adamantyl ester form of tyrphostin AG 957 (Cat. No. 121761) that is shown to be selective and 3 to 4 fold more potent than AG 957 as a ber/abl kinase inhibitor, with a longer half-life *in vivo*. Shown to downregulate $p210^{bcr/abl}$ autokinase activity (IC_{50} = 14 µM). *Purity: ≥97% by HPLC.*

Cat. No. 121762 5 mg $ 170

Ref.: Avramis, I.A., et al. 2002. *Cancer Chemother. Pharmacol.* **50,** 479; Svingen, P.A., et al. 2000. *Clin. Cancer Res.* **6,** 237.

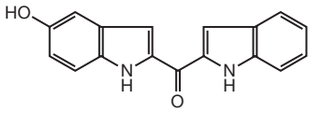
AG 592 (AGL 2592)

A selective, cell-permeable inhibitor of tyrosine kinase activity of EGFR (IC_{50} = 20.3 µM) that is highly effective in inhibiting the growth of Farage cells (IC_{50} = 200 nM) compared to other human malignant cells tested. Irreversibly suppresses the growth of non-Hodgkin's B cell lymphoma cells. Induce apoptosis by blocking tyrosine phosphorylation of Stat3 and enhancing Bcl-2 levels. *Purity: ≥97% by HPLC.*

Cat. No. 658406 5 mg $ 165

Ref.: Ben-Bassat, H., et al. 2002. *J. Pharmacol. Exp. Ther.* **303,** 163; Gazit, A., et al. 1996. *J. Med. Chem.* **39,** 4905.

PDGF Receptor Tyrosine Kinase Inhibitor I (5-Hydroxy-1H-2-indolyl)(1H-2-indolyl)-methanone)

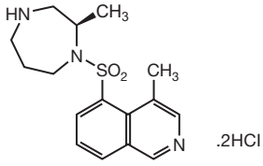


A cell-permeable, highly selective, ATP-competitive inhibitor of the tyrosine kinase activity of PDGF receptor (IC_{50} = 200 nM in Swiss 3T3 cells for PDGFR; IC_{50} = 90 nM *in vitro* and 200 nM in PAE cells for PDGFβ-R; IC_{50} = 1 mM for PDGFα-R). Also inhibits Flt-3 tyrosine kinase 3 activity (IC_{50} = 300 nM for hPDGFβ-R-mFlt-3). *Purity: ≥97% by HPLC.*

Cat. No. 521230 1 mg $ 130

Ref.: Teller, S., et al. 2002. *Leukemia* **16,** 1528; Mahboobi, S., et al. 2002. *J. Med. Chem.* **45,** 1002.

Rho-Kinase Inhibitor (H-1152)



A cell-permeable, highly specific, potent, and ATP-competitive inhibitor of Rho-associated kinase (ROCK; K_i = 1.6 nM). Has only a weak activity against PKA and PKC (K_i = 630 nM and 9.27 µM, respectively). *Purity: ≥95% by HPLC.*

Cat. No. 555550 1 mg $ 145

Ref.: Ikenoya, M., et al. 2002. *J. Neurochem.* **81,** 9; Sasaki, Y., et al. 2002. *Pharmacol. Ther.* **93,** 225.

Casein Kinase II Inhibitor (4,5,6,7-Tetrabromobenzotriazole)

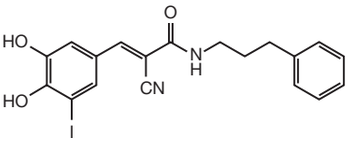
A cell-permeable, highly selective, ATP/GTP-competitive inhibitor of casein kinase-2 (IC_{50} = 900 nM and 1.6 µM, for rat liver and human recombinant enzyme respectively). Its specificity has been demonstrated using a panel of 33 kinases, including PKA, PKB, PKC, MKK1, Erk2, p38, JNK, Lck, Lyn, and Syk. *Purity: ≥97% by HPLC.*

Cat. No. 218697 10 mg $ 70

Ref.: Borowski, P., et al. 2003. *Eur. J. Biochem.* **270,** 1645; Zien, P., et al. 2003. *Biochem. Biophys. Res. Commun.* **306,** 129; Szyszka, R., et al. 1995. *Biochem. Biophys. Res. Commun.* **208,** 418.

AG 1387

A 5-iodo analog of tyrphostin AG 555 (Cat. No. 658404) that is more cell-permeable and more potent than AG 555 as an inhibitor of protein tyrosine kinase and DNA topoisomerase I activities. Inhibits the DNA relaxation activity of TOPO I by interacting with and preventing its binding to DNA. *Purity: ≥97% by HPLC.*

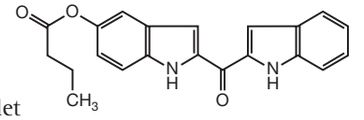


Cat. No. 658520 5 mg $ 80

Ref.: Argaman, M., et al. 2003. *Biochem. Biophys. Res. Commun.* **301,** 789; Aflalo, E., et al. 1994. *Cancer Res.* **54,** 5138; Gazit, A., et al. 1991. *J. Med. Chem.* **34,** 1896.

PDGF Receptor Tyrosine Kinase Inhibitor II [2-(1H-2-Indolylcarbonyl)-1H-5-indolyl]butanoate

A cell-permeable, highly selective, ATP-competitive inhibitor of tyrosine kinase activity of PDGF receptor (IC_{50} = 1.1 µM in Swiss 3T3 cells). Also inhibits Flt-3 activity (IC_{50} = 6.2 µM for hPDGFb-R-mFlt-3). May also serve as a prodrug form of the Platelet Derived Growth Factor Receptor Tyrosine Kinase Inhibitor I (Cat. No. 521230) in cells. *Purity: ≥97% by HPLC.*



Cat. No. 521231 1 mg $ 145

Ref.: Teller, S., et al. 2002. *Leukemia* **16,** 1528; Mahboobi, S., et al. 2002. *J. Med. Chem.* **45,** 1002.

(-)-Terreic Acid, Synthetic

A cell-permeable quinone epoxide antibiotic that acts as a selective inhibitor of Bruton's tyrosine kinase catalytic activity (BTK; IC_{50} = 10 µM and 3 µM for the basal and activation levels, respectively). 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). *Purity: ≥98% by HPLC.*

Cat. No. 581810 2 mg $ 95

Ref.: Kawakami, Y., et al. 1999. *Proc. Natl. Acd. Sci. USA* **96,** 2227; Yamamoto, H., et al. 1980. *Jpn. J. Antibiot.* **33,** 320.

TX-1123

A cell-permeable arylidene-cyclopentenedione derived tyrphostin that inhibits the activity of Src, eEF2-K, and PKA (IC_{50} = 2.2, 3.2, and 9.6 µM, respectively). Exhibits greatly reduced hepatotoxicity. *Purity: ≥95% by HPLC.*

Cat. No. 655200 10 mg $ 85

Ref.: Hori, H., et al. 2003. *Cell. Mol. Biol. Lett.* **8,** 528; Hori, H., et al. 2002. *Bioorg. Med. Chem.* **10,** 3257.

TX-1918

A cell-permeable arylidene-cyclopentenedione derived tyrphostin that inhibits 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. Exhibits greatly reduced hepatotoxicity. *Purity: ≥95% by HPLC.*

Cat. No. 655203 10 mg $ 85

Ref.: Hori, H., et al. 2002. *Bioorg. Med. Chem.* **10,** 3257.

NEW! Raf1 Kinase Inhibitor II (BAY 43-9006)

A cell-permeable bis-aryl urea compound that displays antitumor properties. Acts as a potent inhibitor of Raf1 (IC_{50} = 12 nM) and effectively blocks the Raf/MEK/ERK signaling pathway in tumor cells. *Purity: ≥97% by NMR.*

Cat. No. 553011 1 mg $ 90

Ref.: Bankston, D., et al. 2002. *Org. Proc. Res. Dev.* **6,** 777; Wilhelm, S., and Chien, D.S. 2002. *Curr. Pharm. Des.* **8,** 2255; Lyons, J.F., et al. 2001. *Endocr. Relat. Cancer* **8,** 219.

Have you tried our **NEW!** Phospholipase C Activator?

The first known compound that directly activates PLC

Phospholipase C Activator, *m*-3M3FBS

A novel cell-permeable, sulfonamide compound that acts as a specific activator of phospholipase C (PLC). Stimulate PLC-mediated intracellular Ca^{2+} release, inositol phosphate production, and superoxide generation in various cell types. Activates all isotypes of PLC (β2, β3, γ1, γ2, and δ1) *in vitro*.

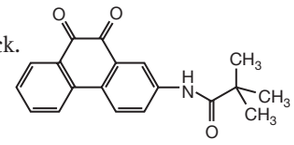
Cat. No. 525185 **10 mg** **$ 65**

Ref.: Bae, Y.S., et al. 2003. *Mol. Pharmacol.* **63,** 1043.

NEW! Protein Tyrosine Phosphatase Inhibitors and Substrate

Protein Tyrosine Phosphatase CD45 Inhibitor

A cell-permeable, potent, selective, competitive, and reversible inhibitor of CD45 (IC_{50} = 200 nM using *p*NPP as the substrate, 3.8 µM for CD45 Lck. >30 µM for PTP1B Lck). *Purity: ≥97% by HPLC.*

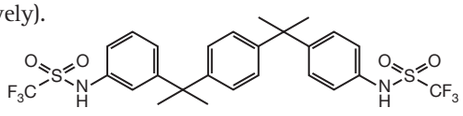


Cat. No. 540215 **1 mg** **$ 125**

Ref.: Urbanek, R.A., et al. 2001. *J. Med. Chem.* **44,** 1777.

Protein Tyrosine Phosphatase Inhibitor IV

An uncharged, 1,4-di-substituted, phenyl-linked *bis*-trifluoromethylsulfonamido (TFMS) phosphate mimic that acts as a potent, reversible, substrate 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-ε, PTP-Meg-2, PTP-σ, PTP-β, and PTP-µ, respectively).
Purity: ≥95% by HPLC.



Cat. No. 540211 **10 mg** **$ 80**

Ref.: Huang, P., et al. 2003. *Bioorg. Med. Chem.* **11,** 1835.

Sodium Stibogluconate

A pentavalent antimony compound that irreversibly inhibits protein tyrosine phosphatase activity (PTPase), including Src homology PTPase-1 (SHP-1) by forming a stable complex. At higher concentrations, the compound inhibits SHP-2 and PTP1B activities; however, it does not have any significant effect on mitogen-activated protein kinase phosphatase-1 (MKP1).
Purity: ≥90% by titration.

Cat. No. 567565 **1 g** **$ 70**

Ref.: Wortmann, G., et al. 2002. *Clin. Infect. Dis.* **35,** 261; Pathak, M.K., and Yi, T. 2001. *J. Immunol.* **167,** 3391.

Protein Tyrosine Phosphatase Substrate III [MCA-EDAEpYAAK(DNP)R-NH_2]

A specific and extremely sensitive fluorescence resonance energy transfer (FRET) substrate for protein tyrosine phosphatases (PTPs). This peptide sequence is similar to that around the phosphotyrosine residue in $pp60^{src}$, the Rous sarcoma virus-transforming protein. Fluorescence intensity of the substrate is unchanged following PTP-catalyzed dephosphorylation, however, it increases by about 12-fold upon subsequent treatment with chymotrypsin, which cleaves only the dephosphorylated substrate at Tyr-Ala bond. *Purity: ≥98% by HPLC.* Exc. max.: ~328 nm; Em. max.: ~395 nm.

Cat. No. 539740 **500 µg** **$ 88**

Ref.: Nishikata, M., et al. 1999. *Biochem. J.* **343,** 385.

NEW! Angiogenesis Research Tools

Meprin A, Rat Kidney

A zinc metalloproteinase, transmembrane protein that degrades several basement membrane proteins including type IV collagen, laminin, and fibronectin. Higher levels of meprin have been reported in colorectal cancer. *Purity: ≥90% by SDS-PAGE.*

Cat. No. 445001 5 µg $ 195

Ref.: Bertenshaw, G.P., et al. 2003. *J. Biol. Chem.* **278,** 2522; Rösmann, S., et al. 2002. *J. Biol. Chem.* **277,** 40650; Sterchi, E.E., et al. 1988. *Arch. Biochem. Biophys.* **265,** 105.

MMP-3 Inhibitor VII

A potent nonpeptide inhibitor of MMP-3 (stromelysin; IC_{50} = 25 nM against the catalytic domain). *Purity: ≥95% by HPLC.*

Cat. No. 444280 1 mg $ 95

Ref.: Hajduk, P.J., et al. 1997. *J. Am. Chem. Soc.* **119,** 5818.

TAS-301 [3-bis(4-Methoxyphenyl)methylene-2-indolinone]

A cell-permeable indolinone compound that displays anti-proliferative properties. Potently inhibits growth factor-induced 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. *Purity: ≥95% by HPLC.*

Cat. No. 608050 10 mg $ 90
25 mg $ 195

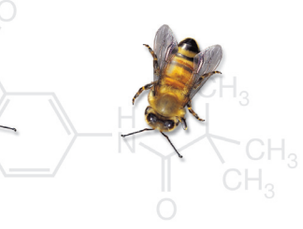
Ref.: Sasaki, E., et al. 2001. *Pharmacology* **63,** 17; Sasaki, E., et al. 2000. *J. Pharmacol. Exp. Ther.* **295,** 1043; Sasaki, E., et al. 2000. *Jpn. J. Pharmacol.* **84,** 252.

VEGF Receptor 2 Kinase Inhibitor III (SU5416)

A cell-permeable, selective, ATP-competitive inhibitor of VEGF-R (KDR/Flk-1) and PDGF-R tyrosine kinases (IC_{50} = 1.04 µM and 20.26 µM in NIH3T3 cells overexpressing Flk-1; K_m = 530 nM for ATP). Also potently inhibits the proliferation of HUVECs induced by VEGF, βFGF, and ECGS (IC_{50} = 50 nM, 5.3 µM and 30.5 µM, respectively). Blocks the autophosphorylation of internal tandem duplication (ITD) and wild-type FLT-3 (IC_{50} = 100 nM). *Purity: ≥97% by HPLC.*

Cat. No. 676487 1 mg $ 110

Ref.: Yee, K.W., et al. 2002. *Blood* **100,** 2941; Mendel, D.B., et al. 2000. *Clin. Cancer Res.* **6,** 4848; Fong, T.A., et al. 1999. *Cancer Res.* **59,** 99; Sun, L., et al. 1999. *J. Med. Chem.* **42,** 5120.



VEGF Receptor 2 Kinase Inhibitor IV

A 3,6-diaryl substituted pyrazolopyrimidine that acts as a potent, ATP-competitive inhibitor of VEGFR-2 (KDR/Flk-1; IC_{50} = 19 nM). Displays ~2-fold greater selectivity for VEGFR-2 over PDGFRβ (IC_{50} = 34 nM) and 10-fold greater selectivity over VEGFR-1 (Flt-1) and VEGFR-3 (Flt-4; IC_{50} = 190 nM). *Purity: ≥95% by HPLC.*

Cat. No. 676489 1 mg $ 70

Ref.: Fraley, M.E., et al. 2002. *Bioorg. Med. Chem. Lett.* **12,** 2767.

VEGF Receptor 3 Kinase Inhibitor, MAZ51

A cell-permeable 3-substituted indolin-2-one compound that acts as an ATP-competitive VEGF receptor tyrosine kinase inhibitor. At low concentration (≤ 5 µM), it specifically blocks VEGF-C and VEGF-D-induced phosphorylation of VEGFR-3, but not VEGFR-2, in PAE cells. *Purity: ≥97% by HPLC.*

Cat. No. 676492 10 mg $ 85

Ref.: Kirkin, V., et al. 2001. *Eur. J. Biochem.* **268,** 5530

Add Reliability and Convenience to Your Research in Cancer Biology

Cell Invasion Assay Kit (24-well)

A convenient and useful assay kit for the quantitation of cell invasion. Contains 12 cell culture inserts with an 8 mm polycarbonate membrane which is coated with a thin layer of a biological matrix that prevents noninvasive cells from going through the membrane. Cells are quantified utilizing a highly sensitive fluorescent dye (Exc. max.: ~485 nm; Em. max.: ~520 nm). Kit contains a 24-well plate containing 12 cell culture inserts coated with basement membrane extract, cell detachment solution, cell staining solution, cell staining diluent, and a directional insert.

Cat. No. QIA129 **1 kit** **$ 325**

Active MMP-13 ELISA Kit

Specifically detects activated MMP-13 in human samples. Kit contains: Coated microtiter plate, assay buffer, wash buffer concentrate, standard, serum standard diluent, detection solutions, conjugate solution, TMB substrate, stop solution, and a directional insert.

Cat. No. QIA130 **1 kit** **$ 525**

Tissue Factor ELISA Kit

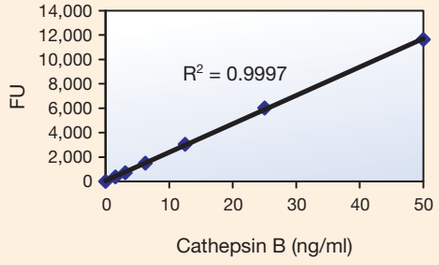
A convenient 96-well format kit for quantitation of tissue factor. Kit contains: Coated micro-test strips, tissue factor standards, standard diluent, detection antibody, detection antibody diluent, TMB substrate, PBS, detergent, and a directional insert. Suitable for use with plasma, serum, cell culture supernatants, or other biological fluids.

Cat. No. QIA132 **1 kit** **$ 495**

InnoZyme™ Cathepsin B Activity Assay Kit, Fluorogenic

A sensitive fluorogenic assay for cathepsin B activity (Exc. max.: ~360-380 nm; Em. max.: ~430-460 nm). The kit contains: cathepsin B, calibration standard, cathepsin B substrate, assay buffer, cathepsin B inhibitor, reduction reagent, cell lysis buffer, microtiter plate, plate sealer, and a directional insert.

Cat. No. CBA001 **1 kit** **$ 315**



InnoZyme™ Cathepsin D Immunocapture Activity Assay Kit, Fluorogenic

A highly selective fluorometric assay for the assay of human cathepsin D activity. Activity is detected with an internally quenched fluorescent substrate (Exc. max.:~328 nm; Em. max: ~393 nm). The kit contains: coated microtiter plate, substrate, cathepsin D standard, assay buffer, sample buffer, plate wash buffer, plate sealer, and a directional insert.

Cat. No. CBA002 **1 kit** **$ 440**

InnoZyme™ Gelatinase Activity Assay kit, Fluorogenic

A sensitive fluorogenic assay (Exc. max: ~325 nm; Em. max.: ~393 nm) for the measurement of gelatinases (MMP-2 and MMP-9). The kit contains: gelatinase substrate, pro-MMP-2 positive control, inhibitor, APMA, assay buffer, microtiterplate, plate sealer, and a directional insert.

Cat. No. CBA003 **1 kit** **$ 375**

NEW! Substrates for Secretases

γ-Secretase Substrate, Fluorogenic [NMA-GGVVIATVK(DNP)-DRDRDR-NH_2]

An internally quenched fluorogenic peptide substrate containing the C-terminal amyloid β-peptide precursor protein amino acid sequence that is cleaved by γ-secretase. Shown to be sensitive and useful for assaying γ-secretase activity. The proteolysis at the $Aβ_{40}$-, $Aβ_{42}$-, and $Aβ_{43}$-cleavage sites results in enhanced fluorescence. *Purity: ≥95% by HPLC.*

Cat. No. 565764 **1 mg** **$ 90**

Ref.: Farmery, M.R., et al. 2003. *J. Biol. Chem.* **278,** 24277.

β-Secretase Substrate VII, Fluorogenic (Abz-VKM~DAE-EDDnp)

An internally quenched fluorogenic peptide substrate designed from wild-type β-amyloid precursor protein sequence that detects BACE1 (β-secretase 1), BACE2, and cathepsin D. Cleavage occurs between Met~Asp residues and results in fluorescence enhancement. *Purity: ≥97% by HPLC.*

Cat. No. 565782 **1 mg** **$ 90**

Ref.: Andrau, D., et al. 2003. *J. Biol. Chem.* **278,** 25859.

β-Secretase Substrate VIII, Fluorogenic (Abz-VNL~DAE-EDDnp)

An internally quenched fluorogenic peptide substrate designed from Swedish mutated β-amyloid precursor protein sequence that specifically detects the activity of BACE1 (β-secretase 1) and BACE2, but not that of cathepsin-D, ADAM-10, TACE, PS1, or PS2. Cleavage occurs between Leu~Asp residues and results in enhanced fluorescence. *Purity: ≥97% by HPLC.*

Cat. No. 565783 **1 mg** **$ 90**

Ref.: Andrau, D., et al. 2003. *J. Biol. Chem.* **278,** 25859.

NEW! Antibodies for Alzheimer's Disease Research

Product	Cat No.	Comments	Size	US $
Anti-mAPH-$1a^L$, Human and Mouse (Rabbit)	PC728	Detects the ~30 kDa mAPH-$1a^L$, a mammalian homolog of the *C. elegans* Anterior pharynx-defective-1 protein. mAPH-1 interacts with presenilin and nicastrin and is suggested to be a functional component of the γ-secretase complex that is required for the intramembrane proteolysis of APP and Notch. **IB, IP**	100 µl	275
Anti-IDE, N-Terminal (97-273), Rat (Rabbit)	PC730	Recognizes the ~115 kDa endogenous IDE as well as recombinant rat IDE. IDE is a neutral, thiol-dependent, cytosolic, zinc metalloprotease that is reported to break down β-amyloid. **ELISA, IB, IC**	100 µl	265
Anti-Cleaved Notch 1 (Val^{1744}), Human (Rabbit)	ST1028	Detects the ~110 kDa Notch 1 cleaved at (Val^{1744}). Notch 1 can be cleaved at this site by furin-like convertase and γ-secretase. This fragment translocates to the nucleus and activates Notch-related transcription. **ELISA, IB, IP**	50 µl	195
Anti-PEN-2, N-Terminal, Human (Rabbit)	NE1008	Detects the ~10 kDa integral membrane protein PEN-2. PEN-2 is reported to physically interact with presenillin 1 and be necessary for γ-secretase activity. **IB, IP**	50 µl	190
Anti-β-Amyloid Precursor-Like Protein 1, N-Terminal, Human/ Mouse (Rabbit)	NE1009	Specifically recognizes APLP1. Does not react with APP and APLP2. APLP1 is a member of the APP family that like APP is processed by γ-secretase in a presenillin-1 dependent manner. **IB, IP**	100 µl	195
Anti-Tau, Phospho-Specific (Ser^{356}), Human (Rabbit)	NE1005	Detects Tau protein phosphorylated on Ser^{356} that can be phosphorylated by GSK-3β, PKA, and MAP kinase. Phosphorylation at Ser^{356} has been found to be a major site in Alzheimer's disease. **IB**	10 T	315

***Key: ELISA:** Enzyme-Linked Immunosorbent Assay; **IB:** Immunoblotting; **IC:** Immunocytochemistry: **IP:** Immunoprecipitation

Note: 1 T = 1 Test

NEW! Phospho-specific Antibodies to Insulin Receptor Substrate 1

Most effects of insulin on biological processes are mediated by the cellular substrates of the insulin receptor (IR), insulin receptor substrates 1 and 2 (IRS-1 and IRS-2). They in turn mediate insulin signaling by recruiting SH2 proteins such as the p85 regulatory subunit of PI-3 kinase through its multiple tyrosine phosphorylation sites. In the unstimulated state IRS-1 is phosphorylated mainly on serine/threonine residues, however, following insulin stimulation tyrosine residues are phosphorylated. Phosphorylations at serine/threonine residues are reported to antagonize some of the responses induced by insulin. For example, TNF-α, a key mediator in several insulin resistance models, increases phosphorylation of IRS-1 on serine residues and antagonizes insulin-stimulated tyrosine phosphorylation of IRS-1 in adipocytes. Hence, modification of IRS-1 can have a deleterious effect on insulin resistance in diabetes.

Product	Cat No.	Comments	Size	US $
Anti-Insulin Receptor, Phospho-Specific (Tyr^{972}), Human (Rabbit)	GF1000	Detects the ~95 kDa β-subunit of the insulin receptor phosphorylated on Tyr^{972}. This phosphorylation site is alternatively numbered Tyr^{960} in some references. Phosphorylation at Tyr^{972} is required for the binding and/or phosphorylation of adaptor proteins such as Shc, IRS-1, PI 3-kinase, and SOCS. **IB**	10 T	315
Anti-IRS-1, Phospho-Specific (Ser^{616}), Human (Rabbit)	GF1001	Detects the ~165 kDa IRS-1 phosphorylated on Ser^{616} that is phosphorylated by a protein activated by protein kinase C. Phosphorylation on Ser^{616} results in the inhibition of insulin signaling in the cell. May detect two additional lower molecular weight bands. **IB, IC**	10 T	315
Anti-IRS-1, Phospho-Specific (Tyr^{896}), Human (Rabbit)	GF1003	Detects the ~165 kDa IRS-1 phosphorylated on Tyr^{896}. Tyr^{896} of IRS-1 is a Grb2 SH2 domain binding site. **IB**	10 T	315
Anti-IRS-1, Phospho-Specific (Tyr^{941}), Human (Rabbit)	GF1004	Detects the ~165 kDa IRS-1 phosphorylated on Tyr^{941}. Inhibition of phosphoinositide 3-kinase enhances the Tyr^{941} phosphorylation of IRS-1. **IB**	10 T	315
Anti-IRS-1, Phospho-Specific (Tyr^{1229}), Human (Rabbit)	GF1002	Detects the ~165 kDa IRS-1 phosphorylated on Tyr^{1229}. Tyr^{1229} of IRS-1 is a SHP-2 binding site, which serves to negatively regulate insulin signaling. **IB**	10 T	315
Anti-IRS-1, Phospho-Specific (Ser^{307}), Mouse (Rabbit)	GF1005	Detects the ~165 kDa IRS-1 phosphorylated on Ser^{307}, which is reported to block interactions with the insulin receptor and inhibit insulin action. **IB**	100 µg	295
Anti-IRS-1, Phospho-Specific (Tyr^{608}), Mouse (Rabbit)	GF1006	Detects the ~165 kDa IRS-1 phosphorylated on Tyr^{608}. Tyr^{608} is reported to be mutated in a type II diabetics contributing to insulin resistance by impairing signaling through PI 3-kinase-dependent pathways. **IB**	100 µg	295
Anti-IRS-1, Phospho-Specific (Ser^{636}), Mouse (Rabbit)	GF1007	Detects the ~165 kDa IRS-1 phosphorylated on Ser^{636}. Increased phosphorylation of IRS-1 on Ser^{636} is reported in the primary culture of skeletal muscle cells from diabetic patients. **IB**	100 µg	295

Key: IB: Immunoblotting; **IC:** immunocytochemistry. **Note:** 1 T = 1 Test

Also Available...

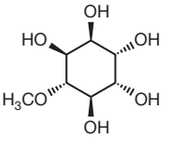
GW501516

A cell-permeable thiazolyl compound that acts as a potent, high-affinity PPARδ agonist (EC_{50}= 1.1 and 20 nM for human and murine PPARδ, respectively). Exhibits greater selectivity toward δ over other PPAR subtypes (EC_{50}= 1.1 and 0.85 µM for human PPARα and γ, respectively).
Purity: ≥97% by NMR.

Cat. No. 370710 1 mg $ 150

Ref.: Sznaidman, M.L., et al. 2003. *Bioorg. Med. Chem. Lett.* **13,** 1517; Wang, Y.X., et al. 2003. *Cell* **113,** 159; Oliver, Jr. W.R., 2001. *Proc. Natl. Acad. Sci. USA* **98,** 5306.

D-Pinitol



A naturally occurring 3-methoxy analog of D-*chiro*-inositol that mimics the effects of insulin. Reported to lower blood glucose levels in streptozotocin-induced or alloxan diabetic rats and in normal rats given glucose. Increases glucose and basal 2-deoxyglucose uptake by L6 muscle cells. Suggested to interact with the insulin-glucose transport signaling pathway. *Purity: ≥90% by HPLC.*

Cat. No. 527970 500 mg $ 60

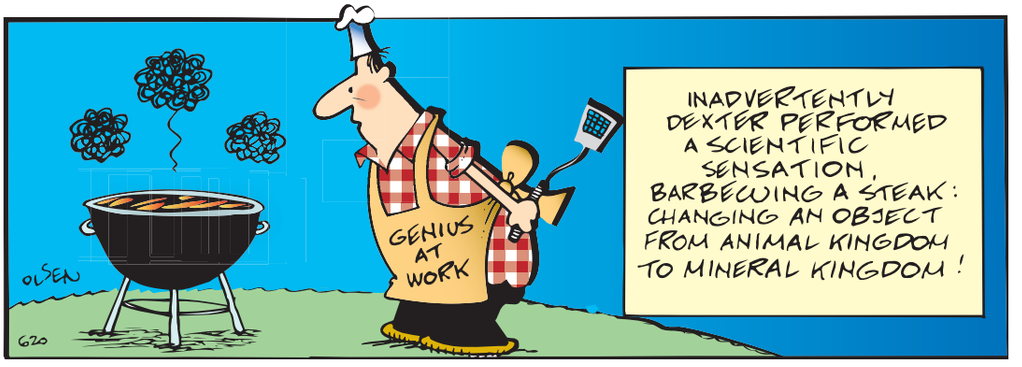
Ref.: Bates, S.H., et al. 2000. *Br. J. Pharmacol.* **130,** 1944; Davis, A., et al. 2000. *Diabetes Care* **23,** 1000; Narayanan, C.R., et al. 1987. *Curr. Sci.* **56,** 139.

Capture your kinases, proteases, and other proteins with our new Line of Immobilized Inhibitors

These inhibitors are covalently bound to acrylic beads and serve as functional ligands that selectively interact with the active site of enzymes in cell lysates or tissue extracts. These affinity precipitation beads are useful in capturing up-regulated target proteins, which interact with immobilized inhibitor ligands. Due to their selective nature, these immobilized inhibitors are also useful tools in affinity purification of target proteins.

Product	Cat No.	Comments	Size*	US $
1400W Immobilized	100051	A selective iNOS inhibitor (1400 W, Cat. No. 100050) covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. *Binding capacity: ≥ 0.5 mg NOS per gram of dry beads (as determined for constitutive rat brain NOS).*	1 Set	125
E-64, Immobilized	324891	A cysteine protease inhibitor (E-64, Cat. No. 324890) covalently attached to hydrophilic acrylic beads via a 4-carbon spacer. *Binding capacity: ≥ 2 mg purified cathepsin B per gram of dry beads.*	1 Set	165
H-9, Immobilized	371966	A protein kinase G inhibitor (H-9, Cat. No. 371961) covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. *Binding capacity: ≥ 1 mg purified PKG per gram of dry beads.*	1 Set	125
Ro 31-7549, Immobilized	557509	A protein kinase C inhibitor Ro 31-7549 (Cat. No. 557508) covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. *Binding capacity: ≥3 mg purified PKC_α per gram of dry beads.*	1 Set	125
Roscovitine, Immobilized	557361	A cyclin-dependent kinase inhibitor (Roscovitine, Cat. No. 557360) covalently attached to hydrophilic acrylic beads via a 3-carbon spacer.	1 Set	125
SB202190, Immobilized	559403	A p38 MAP kinase inhibitor (SB202190, Cat. No. 559388) covalently attached to hydrophilic acrylic beads via a 3-carbon spacer. *Binding capacity: ≥ 1 mg p38 MAP kinase per gram of dry beads (as determined for recombinant GST-p38).*	1 Set	125
W-7, Immobilized	681630	A calmodulin antagonist (W-7, Cat. No. 681629) covalently attached to hydrophilic acrylic beads via an 8-carbon spacer. *Binding capacity: ≥ 2 mg purified calmodulin per gram of dry beads (bovine brain calmodulin).*	1 Set	125

*Control beads are included in each set



NEW! Protease Inhibitors

Cathepsin L, Inhibitor VI [N-(4-Biphenylacetyl)-S-methylcysteine-(D)-Arg-Phe-β-phenethylamide]

An end-protected tripeptide that acts as a highly selective, potent, and reversible inhibitor of cathepsin-L (K_i = 19 nM, human recombinant). Resists proteolysis by cathepsin L and mimics the mode of autoinhibition of procathepsin L. Displays greater selectivity for cathepsin L over cathepsin K (K_i = 5.9 µM) and cathepsin B (K_i = 4.1 µM) *Purity: ≥97% by HPLC.*

Cat. No. 219495 **5 mg** **$ 80**

Ref.: Chowdhury, S.F., et al. 2002. *J. Med. Chem.* **45,** 5321.

Dipeptidylpeptidase II Inhibitor (L-2,4-Diaminobutyrylpiperidinamide)

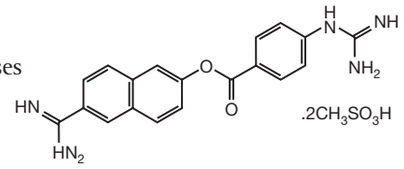
A potent and highly specific inhibitor of dipeptidylpeptidase II (IC_{50} = 130 nM) that displays > 7,700-fold greater selectivity for DPP II over DPP IV (IC_{50} >1 mM). *Purity: ≥97% by HPLC.*

Cat. No. 317621 **10 mg** **$ 80**

Ref.: Senten, K., et al. 2002. *Bioorg. Med. Chem. Lett.* **12,** 2825.

FUT-175

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. *Purity: ≥97% by HPLC.*



Cat. No. 344960 **5 mg** **$ 135**

Ref.: Kam, C.M., et al. 2000. *Biochim. Biophys. Acta* **1477,** 307; Pfeifer, P.H., et al. 1999. *Clin. Chem.* **45,** 1190; Poe, M., et al. 1991. *Arch. Biochem. Biophys.* **284,** 215; Ikari, N., et al. 1983. *Immunology* **49,** 685.

NEW! Calpain Inhibitors

Calpain Inhibitor X [Z-L-Abu-CONH-ethyl]

A cell-permeable dipeptidyl α-ketoamide that acts as a potent, reversible, active site inhibitor of calpains-1 and -2 (K_i ~ 250 nM). *Purity: ≥95% by HPLC.*

Cat. No. 208742 **1 mg** **$ 80**
5 mg **$ 280**

Ref.: James, T., et al. 1998. *J. Neurosci. Res.* **51,** 218; Li, Z., et al. 1993. *J. Med. Chem.* **36,** 3472.

Calpain Inhibitor XI [Z-L-Abu-CONH$(CH_2)_3$-morpholine]

A cell-permeable dipeptidyl α-ketoamide that acts as a potent, highly selective, reversible, active site inhibitor of calpains-1 and -2 (K_i = 140 nM and 41 nM, respectively). *Purity: ≥95% by HPLC.*

Cat. No. 208743 **1 mg** **$ 80**
5 mg **$ 280**

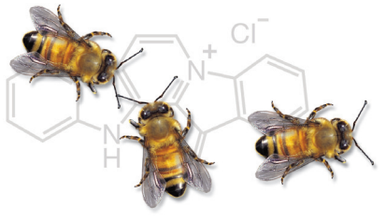
Ref.: Blomgren, K., et al. 2001. *J. Biol. Chem.* **276,** 10191; Blomgren, K., et al. 1999. *J. Biol. Chem.* **274,** 14046; Li, Z., et al. 1996. *J. Med. Chem.* **39,** 4089.

Calpain Inhibitor XII (Z-L-Nva-CONH-CH_2-2-Py)

A cell-permeable dipeptidyl α-ketoamide compound that acts as a potent, selective, reversible, active site inhibitor of calpain-1 (K_i = 19 nM). Shown to inhibit calpain-2 (K_i = 120 nM) and cathepsin B, human (K_i = 750 nM) at higher concentrations. *Purity: ≥95% by HPLC.*

Cat. No. 208744 **1 mg** **$ 80**
5 mg **$ 280**

Ref.: Lokuta, M.A., et al. 2003. *Proc. Natl. Acad. Sci. USA* **100**, 4006; Li, Z., et al. 1996. *J. Med. Chem.* **39,** 4089.



PYY$_{3-36}$, Human (H-IKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY-NH$_2$)

A gut hormone of the neuropeptide Y family that acts as an appetite regulator and as a high affinity Y2R (NPY Y2 receptor) agonist. *Purity: ≥98% by HPLC.*

Cat. No. 551451 1 mg $ 170

Ref. Batterham, R.L., et al. 2002. *Nature* **418,** 650; Keire, D.A., et al. 2000. *Am. J. Physiol. Gastrointest. Liver Physiol.* **279,** G126; Grandt, D., et al. 1994. *Regl. Pept.* **51,** 151.

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p75^{NTR} Signaling Inhibitor, Pep5 (H-CFFRGGFFNHNPRYC-OH, Cyclic)

A 15-mer cyclic peptide that acts as a specific blocker of growth inhibition mediated by neurotrophin receptor p75^{NTR}. Prevent the activation of RhoA by associating with p75^{NTR} and disrupting its interaction with Rho-GDI (Rho GDP dissociation inhibitor). *Purity: ≥97% by HPLC.*

Cat. No. 506180 1 mg $ 145

Ref.: Yamashita, T., and Tohyama, M. 2003. *Nat. Neurosci.* **6,** 461.

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p75^{NTR} Signaling Inhibitor, Cell-permeable, TAT-Pep5

The p75^{NTR} inhibitor Pep5 (Cat. No. 506180) is made cell-permeable by fusing it with the N-terminal protein transduction domain sequence (11 amino acid) from HIV protein TAT. A blocker of MAG- and Nogo-induced inhibition of neurite outgrowth in both dorsal root ganglion and postnatal cerebellar neurons. *Purity: ≥97% by HPLC.*

Cat. No. 506181 500 µg $ 145

Ref.: Yamashita, T., and Tohyama, M. 2003. *Nat. Neurosci.* **6,** 461; Schwarze, S.R., et al. 1999. *Science* **285,** 1569.

PK 11195

A specific antagonistic ligand for peripheral benzodiazepine receptors (PBR). Does not bind to other known neurotransmitter receptors. *Purity: ≥95% by NMR.*

Cat. No. 528155 5 mg $ 55

Ref.: Wala, E.P., et al. 2000. *Pharmacol. Res.* **41,** 461; Valtier, D., et al. 1987. *Neuropharmacology* **26,** 549.

Riluzole

A potent inhibitor of glutamate release and blocker of Na^+ channels. Stimulates the synthesis of NGF, BDNF, and GDNF in mouse astrocyte culture. *Purity: ≥97% by HPLC.*

Cat. No. 557324 50 mg $ 75

Ref.: Schiefer, J., et al. 2002. *Mov. Disord.* **17**, 748; Mizuta, I., et al. 2001. *Neurosci. Lett.* **310,** 117; Mizoule, J., et al. 1985. *Neuropharmacology* **24,** 767.

NEW! Cathepsin Substrate

Cathepsin D/E Substrate, Fluorogenic [MOCAc-GKPILF~FRLK(Dnp)-D-R-NH$_2$]

An internally quenched fluorogenic substrate for cathepsins D and E (k_{cat}/K_m = 15.6 µM^{-1}s^{-1} and 10.9 µM^{-1}s^{-1} for rat gastric cathepsin D and human erythrocyte cathepsin E, respectively). Cleavage occurs between Phe~Phe residues. *Purity: ≥97% by HPLC.*

Cat. No. 219360 1 mg $ 175

Ref.: Yasuda, Y., et al. 1999. *J. Biochem.* **126,** 260; Yasuda, Y., et al. 1999. *J. Biochem.* **125,** 1137.