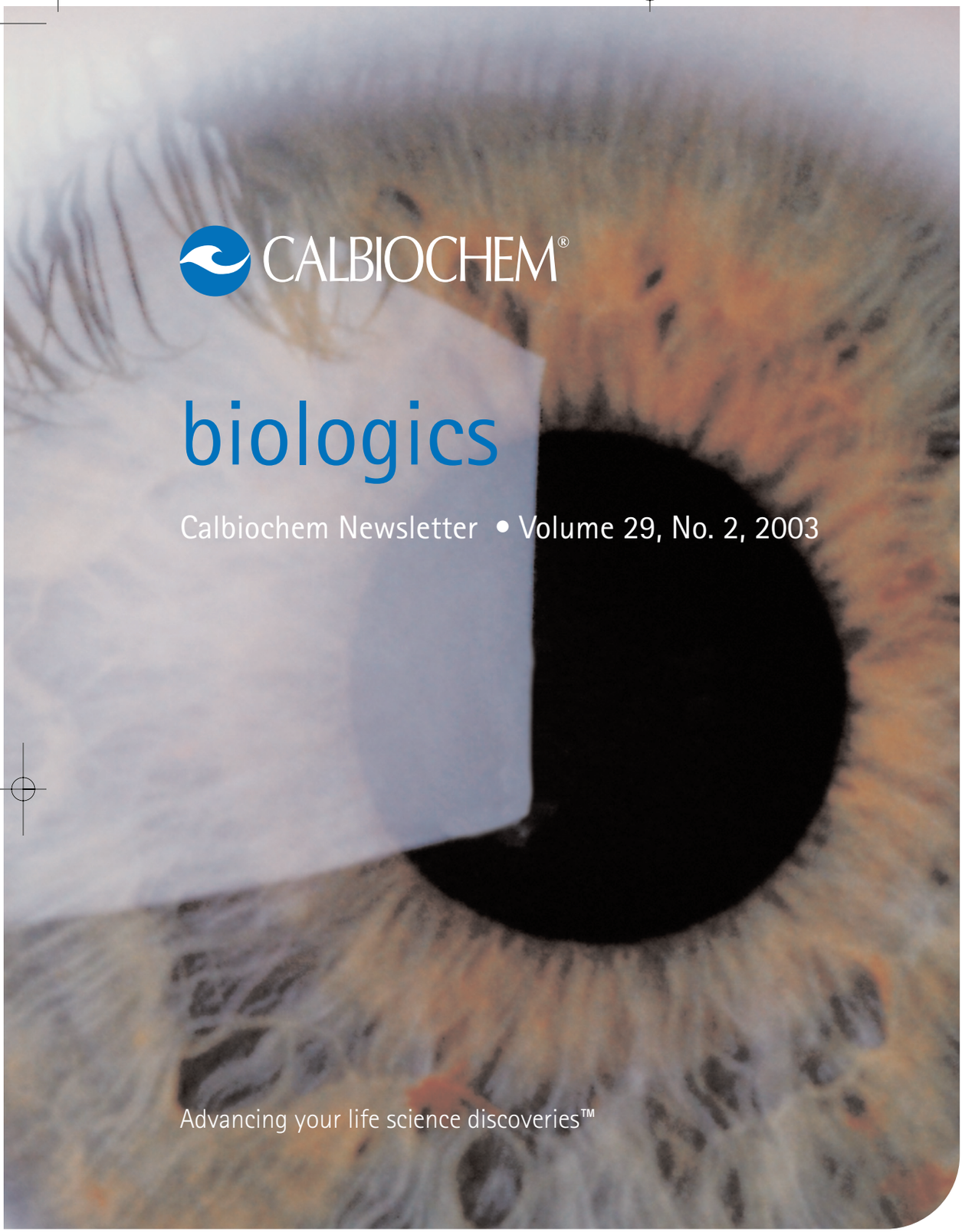

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Calbiochem Newsletter • Volume 29, No. 2, 2003

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Table of Contents

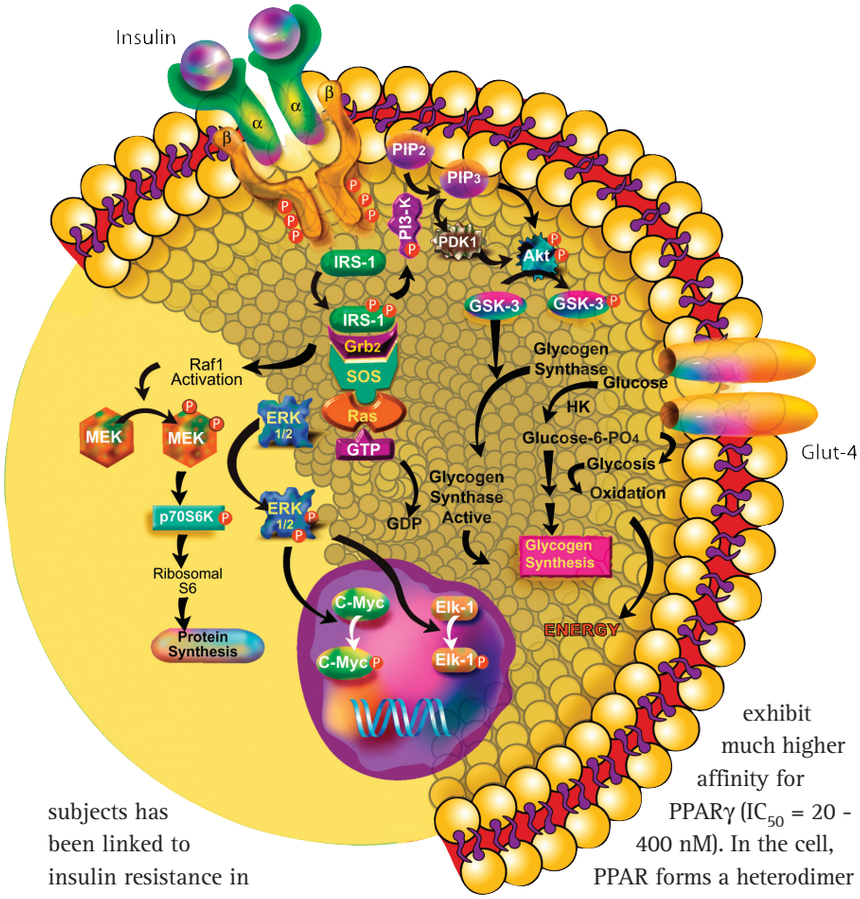
Defective Insulin Signaling in Diabetes

Insulin affects target cells via its interaction with insulin receptor (IR), a heterotetrameric glycoprotein consisting of two extracellular α-subunits (135 kDa) and two transmembrane β-subunits (95 kDa). Insulin binding to the α-subunits stimulates the tyrosine kinase activity of the β-subunits. The kinase domains of the β-subunits are juxtaposed to the α-subunits, which permits autophosphorylation of $Tyr^{1158,1162, \text{ and } 1163}$, the first step in receptor activation. The ability of the IR to autophosphorylate as well as its ability to phosphorylate several intracellular substrates is crucial for its mediation of the cellular responses to insulin. IRs transphosphorylate tyrosine residues on several immediate substrates including insulin receptor substrate (IRS) proteins 1-4, Shc, Grb-2 associated binder-1, and APS adapter protein, all of which provide specific docking sites for other signaling proteins containing SH2 domains. These events lead to the activation of downstream signaling molecules including the PI 3-Kinase (PI 3-K).

PI 3-K plays a critical role in the metabolic actions of insulin. Activated PI 3-K specifically phosphorylates PI substrates to produce PIP_2 and PIP_3, which then enlist PI 3-K-dependent kinase (PDK1) and Akt from the cytoplasm to the plasma membrane. This leads to conformational changes in Akt that gets phosphorylated on Thr^{308} and Ser^{473} by PDK1 and becomes activated. Akt phosphorylates GSK-3 and inactivates it, which allows the activation of glycogen synthase that initiates glycogen synthesis. Activation of Akt translocates glucose transporter 4 (GLUT4) vesicles to the cell membrane where they participate in the transport of glucose.

The internalization of IR also plays an important role in insulin signaling. The activated insulin-IR complex is internalized into endosomes in a tyrosine phosphorylation-dependent manner. The tyrosine kinase of the internalized IR can then phosphorylate several other cytoplasmic substrates. The acidic environment of the endosomal lumen causes dissociation of insulin from the IR, attenuating further phosphorylation events. Insulin is degraded by endosomal insulinase and the IR is dephosphorylated by extralumenal endosome-associated protein tyrosine phosphatases before it is recycled to the cell surface.

Insulin resistance observed in obesity and Type II diabetes results in a variety of metabolic defects, including hyperglycemia, hyperlipidemia, and hyperinsulinemia, which are associated with a decrease in the number of insulin receptors and impaired insulin-stimulated recruitment of GLUT4 transporter from its intracellular storage compartment to the cell surface. Adipose tissue plays a vital role in the development of insulin resistance and associated abnormalities. A higher circulating level of free fatty acids (FFA), as in obesity and Type II diabetes, is considered to be an important contributor to insulin resistance. Elevated FFA levels correlate well with impaired insulin-stimulated IRS-1 phosphorylation, PI 3-K activity, and with increased hepatic glucose production. Long-term exposure of pancreatic β-cells to FFAs diminishes their insulin secretory response to glucose. Adipose tissue also secretes a variety of hormones (adipokines) that regulate various cellular processes. Higher expression of TNF-α in adipose tissue of obese



subjects has been linked to insulin resistance in obesity and diabetes. TNF-α is known to impair insulin signaling through IRS-1 serine phosphorylation and through reduced expression of IRS-1 and GLUT4. Deficiency of leptin, another hormone of adipose origin, is also linked with insulin resistance in db/db and ob/ob mice. Leptin replacement improves glycemic control and reduces circulating lipid levels. Resistin, another hormone of adipose origin, is found at much higher levels in animal models of diabetes and obesity, and treatments with insulin sensitizing agents, such as thiazolidinediones (TZDs), reduces circulating levels of resistin.

TZDs belong to a new class of insulin sensitizers and are under clinical trials for the treatment of Type II diabetes. They act as direct, high-affinity ligands of peroxisome proliferator-activated receptor γ (PPARγ). Although PPAR is expressed in most organs, the level of PPAR mRNA is about 50-fold higher in adipose tissue. When compared to some natural ligands, such as 15-deoxy-Δ 12, 14-prostaglandin J_2, TZDs exhibit much higher affinity for PPARγ (IC_{50} = 20 - 400 nM). In the cell, PPAR forms a heterodimer with the retinoid X receptor (RXR). When induced by TZDs, a conformational change occurs in the heterodimer and co-repressor complexes are displaced. This promotes binding of the PPAR-RXR complex to PPAR response elements (PPRE) in target genes, resulting in modification of the transcription of these genes. PPREs are commonly found in genes involved in lipid metabolism and energy balance, including those encoding lipoprotein lipase, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, glucokinase, and glucose transporter GLUT4.

References:
Haber, E.P. et al. 2003. *J. Cell Physiol.* **194**, 1; Albrektsen, T., et al. 2002. *Diabetes* **51**, 1042; Arner, P.2002. *Diabetes Metab. Res. Rev.* **18**, S5; Hauner, H. 2002. *Diabetes Metab. Res. Rev.* **18**, S10; Jiang, G., and Zhang, B.B. 2002. *Front. Biosci.* **7**, 903; Stumvoll, M., and Haring, H.U. 2002. *Ann. Med.* **34**, 217; Whiteman, E.L., et al. 2002. *Trends Endocinol. Metab.* **13**, 444; Bevan, P. 2001. *J. Cell Sci.* 114, 1429; Lawlor, M.A., and Alessi, D.R. 2001. *J. Cell Sci.* **114**, 2903; Saltiel A.R., and Kahn, R. 2001. *Nature* **414**, 799; Authier F, et al. 1998. *Biochem. J.* **332**, 421; Contreres, J.O., et al. 1998. *J. Biol. Chem.* **273**, 22007; Schmid, E., et al. 1998. *FASEB J.* **12**, 863; White, M.F., and Yenush, L. 1998. *Curr. Top. Microbiol. Immunol.* **228**, 179; Withers, D.J., et al. 1998. *Nature* **391**, 900; Hubbard, S.R. 1997. *EMBO J.* **16**, 5573; Mohan, C., and Bessman, S.P. 1989. *Curr. Top. Cell. Regul.* **30**, 105; Rosen, O.M., et al. 1983. *Proc. Natl. Acad. Sci. USA* **80**, 3237.

NEW! Akt Substrates

AKTide-2T (ARKRERTYSFGHHA)

An optimal peptide substrate for assaying Akt activity. The peptide undergoes phosphorylation at the Ser residue (K_m = 3.9 µM). *Purity: ≥95% by HPLC.*

Cat. No. 123900 1 mg $ 80

Ref.: Obata, T., et al. 2000. *J. Biol. Chem.* **275**, 36108.

AKTide-SA (ARKRERAYAFGHHA)

Serves as a negative control for AKTide-2T (Cat. No. 123900). Lacks the phosphorylatable Ser residue. *Purity: ≥95% by HPLC.*

Cat. No. 123905 1 mg $ 80

Ref.: Obata, T., et al. 2000. *J. Biol. Chem.* **275**, 36108.

NEW! GSK-3β Inhibitors

GSK-3β Inhibitor III

(2,4-Dibenzyl-5-oxothiadiazolidine-3-thione)

An oxothiadiazolidine-3-thione analog that acts as a non-ATP competitive inhibitor of GSK-3β (IC_{50} = 10 µM). *Purity: ≥95% by HPLC.*

Cat. No. 361542 1 mg $ 57

Ref.: Martinez, A., et al. 2002. *J. Med. Chem.* **45**, 1292.

Hymenialdisine, *Stylissa damicornis*

A cell-permeable, potent inhibitor of GSK-3β (IC_{50} = 10 nM). Also inhibits MEK-1 (IC_{50} = 6 nM), Cdks (IC_{50} = 22 nM for Cdk1/cyclin B, 40 nM for Cdk2/cyclin E, and 28 nM for Cdk5/p35), and CK1 (IC_{50} = 35 nM). *Purity: ≥97% by HPLC.*

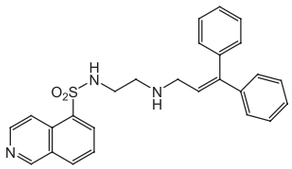
Cat. No. 400085 500 µg $ 191

Ref.: Tasdemir, D., et al. 2002. *J. Med. Chem.* **45**, 529.

Looking for NEW Akt Inhibitors?

NL-71-101

A potent and selective inhibitor of Akt/PKB (IC_{50} = 3.7 µM) that displays 2.4-fold greater selectivity over PKA (IC_{50} = 9 µM). Induces apoptosis in tumor cells overexpressing Akt. *Purity: ≥95% by HPLC.*

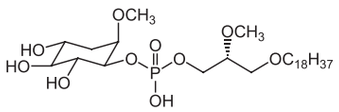


Cat. No. 487940 1 mg $ 84

Ref.: Reuveni, H., et al. 2002. *Biochemistry* **41**, 10304.

Akt Inhibitor II (SH-5)

A novel Akt inhibitor that blocks the activation of Akt without affecting the phosphorylation of PDK-1 and other downsteam kinases. Induces apoptosis in tumor cells expressing high levels of Akt. *Purity: ≥98% by NMR.*

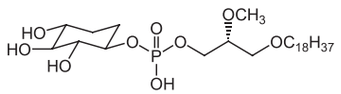


Cat. No. 124008 1 mg $ 228

Ref.: Kozikowski, A.P., et al. 2003. *J. Am. Chem. Soc.* **125**, 1144.

Akt Inhibitor III (SH-6)

A novel Akt inhibitor that blocks the activation of Akt without affecting the phosphorylation of PDK-1 and other downsteam kinases. Induces apoptosis in tumor cells expressing high levels of Akt. *Purity: ≥98% by NMR.*



Cat. No. 124009 1 mg $ 228

Ref.: Kozikowski, A.P., et al. 2003. *J. Am. Chem. Soc.* **125**, 1144.

NEW! Antibodies for Diabetes Research

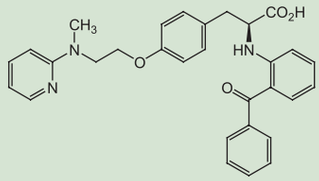
Product	Cat. No.	Comments	Application*	Size	US $
Anti-IGF-I Receptor, α-Subunit, Human (Mouse)	407246	Recognizes the ~125 kDa α-subunit of the human IGF-I receptor, and weakly cross-reacts with rabbit IGF-I receptor.	ELISA, FS, IP, PS	100 µg	232
Anti-Insulin Receptor, Phospho-specific (Tyr^{1158}), Human (Rabbit)	407706	Reacts with the 95 kDa subunit of the phosphorylated receptor in human, mouse, and rat. Cross-reacts with IGF-1 phosphorylated at Tyr^{1131}.	IB	10T	315
Anti-Insulin Receptor, Phospho-specific ($Tyr^{1162,1163}$), Human (Rabbit)	407707	Reacts with the 95 kDa subunit of the phosphorylated receptor in human, mouse, and rat. Cross-reacts with IGF-1 phosphorylated at Tyr^{1135} and Tyr^{1136}.	IB	10T	315
Anti-IRS-1, Rat (Rabbit) Insulin Receptor Substrate	420292	Detects a band at ~185 kDa corresponding to IRS-1. Reacts with human, mouse, and rat.	IB, IP	100 µl	252
Anti-IRS-2, Mouse (Rabbit)	420293	Detects a band at ~180 kDa corresponding to IRS-2. Reacts with hamster, human, mouse, rat.	IB, IP	100 µl	252
Anti-Glycogen Synthase Kinase-3β, Phospho-Specific (Ser^{9}), Human (Mouse)	361527	Recognizes the ~46 kDa GSK-3β phosphorylated at Ser^{9} in human and mouse.	ELISA, IB	1 set	295
Anti-Glucose Transporter-1, Human (Rabbit)	400060	Recognizes the 42 - 45 kDa GLUT1 protein. Also recognizes the Hep G2-type transporter. Reacts with bovine, chicken, human, mouse, porcine, rabbit, and rat.	ELISA, IB, IH, IP	50 µg	224
Anti-Glucose Transporter-2, Rat (Rabbit)	400061	Recognizes the 53 - 61 kDa GLUT2 protein in human, mouse, and rat.	ELISA, IB, FS, IP	50 µg	224
Anti-Glucose Transporter-3, Human (Rabbit)	400062	Recognizes the ~45 kDa GLUT3 protein in cell lysates. Reacts with human.	ELISA, IB, FS, IP	50 µg	224
Anti-Glucose Transporter-3, Rat (Rabbit)	400063	Recognizes the ~45 kDa GLUT3 protein in cell lysates. Reacts with mouse and rat.	ELISA, IB, FS	50 µg	224
Anti-Glucose Transporter-4, Mouse (Rabbit)	400064	Recognizes the ~40 - 43 kDa GLUT4 protein in cell lysates. Reacts with human, mouse, and rat.	ELISA, IB, FS, IP	50 µg	224
Anti-Glucose Transporter-5, Human (Rabbit)	400065	Recognizes the ~50 - 55 kDa GLUT5 protein in cell lysates. Reacts with human.	ELISA, IB, FS	50 µg	224
Anti-Glucose Transporter-5, Rat (Rabbit)	400066	Recognizes the ~60 kDa GLUT5 protein in cell lysates. Reacts with rat.	ELISA, IB, FS	50 µg	224
Anti-Glucose Transporter-7, Rat (Rabbit)	400067	Recognizes the ~52 kDa GLUT7 protein in human and rat.	ELISA, IB, FS, IP	50 µg	224

* **ELISA:** enzyme-linked immunosorbent assay; **FS:** frozen sections; **IB:** immunoblotting; **IH:** immunohistochemistry; **IP:** immunoprecipitation; **PS:** paraffin sections **Note:** 1 T = 1 test

Insulin Sensitizers and Desensitizers: Agonists and Antagonists of Peroxisome Proliferator-Activated Receptors

GW1929

A potent, tyrosine-based PPARγ agonist (EC_{50} = 13 nM for murine receptor and 6.2 nM for human receptor in cell-based transactivation assays). *Purity: ≥95% by HPLC.*



Cat. No. 370695 1 mg $ 235

Ref.: Willson, T.M., et al. 2000. *J. Med. Chem.* **43,** 527; Brown, K.K., et al. 1999. *Diabetes* **48,** 1415.

GW7647

A cell-permeable, potent, and selective agonist of PPARα (EC_{50} = 6 nM for human PPAR α). Exhibits lipid lowering activity in rats. *Purity: ≥98% by HPLC.*

Cat. No. 370698 5 mg $ 150

Ref.: Muoio, D.M., et al. 2002. *J. Biol. Chem.* **277,** 26089; Poirier, H., et al. 2001. *Biochem. J.* **355,** 481; Brown, P.J., et al. 2001. *Bioorg. Med. Chem. Lett.* **11,** 1225.

Pioglitazone, Hydrochloride

A potent, selective activator of PPARγ (EC_{50} = 690 nM) that ameliorates TNF-α-induced insulin resistance and improves insulin-stimulated tyrosine phosphoraylation of insulin receptor/insulin receptor substrate-1 (IR/IRS-1). *Purity: ≥98% by HPLC.*

Cat. No. 528115 25 mg $ 139

Ref.: Qi, N., et al. 2002. *J. Biol. Chem.* **277,** 48501; Goke, R., et al. 2001. *Digestion* **64,** 75; Iwata, M., et al. 2001. *Diabetes* **50,** 1083; Ishizuka, T., et al. 1998. *Diabetes* **47,** 1494.

Pseudolaric Acid B, *Pseudolarix kaempferi*

A cell-permeable activator of PPAR α, γ, and δ (EC_{50} ~ 100 μM). Displays potent antifungal, antimicrobial, and cytotoxic properties.

Cat. No. 539595 1 mg $ 165

Ref.: Jardat, M.S., et al. 2002. *Planta Med.* **68,** 667; Li, E., et al. 1995. *J. Nat. Prod.* **58,** 57; Pan, D.J., et al. 1990. *Planta Med.* **56,** 383.

Z-Guggulsterone

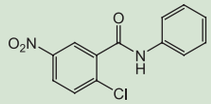
A selective antagonist of farnesoid X receptor (FXR) that inhibits FXR transactivation (IC_{50} = 10 μM in the presence of 100 μM of chenodeoxycholic acid). Does not affect the transactivation of liver X receptor α, PPARγ, and retinoid X receptor α.

Cat. No. 370690 10 mg $ 98 25 mg $ 196

Ref.: Urizar, N.L., et al. 2002. *Science* **296,** 1703; Chander, S., et al. 1996. *Phytotherapy Res.* **10,** 508.

GW9662

A cell-permeable, selective and irreversible PPARγ antagonist (IC_{50} = 3.3 nM, 32 nM, and 2.0 μM for PPARγ, PPARα, and PPARδ, respectively). Covalently modifies a cysteine residue in the binding site of PPAR. At higher concentration (10 μM), also acts as an agonist of human pregnane X receptor and farnesoid X receptor. *Purity: ≥98% by HPLC.*



Cat. No. 370700 5 mg $ 50

Ref.: Leesnitzer, L.M., et al. 2002. *Biochemistry* **41,** 6640; Willson, T.M., et al. 2000. *J. Med. Chem.* **43,** 527; Huang, J.T., et al. 1999. *Nature* **400,** 378.

Also Available....

Product	Cat. No.	Comments	Size	US $
PPARα, Human, Recombinant, *E. coli*	516559	Expressed mainly in skeletal muscle, heart, liver, and kidney and is activated by free fatty acids. Regulates many genes involved in the β-oxidation of fatty acids.	10 KU	325
PPARγ, Human, Recombinant, *E. coli*	516563	Mainly expressed in adipose tissue where it plays a key role in adipocyte differentiation and insulin sensitivity.	10 KU	325
PPARδ, Human, Recombinant, *E. coli*	516564	Highly expressed in lipid-metabolizing tissues. Involved in the regulation of fat transport and insulin sensitivity. Serves as a VLDL sensor in macrophages.	10 KU	325

NEW! MAP Kinase Inhibitor

SB 239063

A potent inhibitor of p38 MAP Kinase (IC_{50} = 44 nM for recombinant purified human p38α). *Purity: ≥97% by HPLC.*

Cat. No. 559404 500 μg $ 98

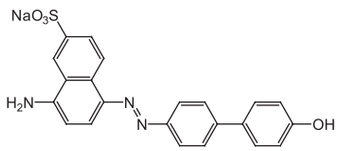
Ref.: Legos, J.J., et al. 2002. *Eur. J. Pharmacol.* **447,** 37; Underwood, D.C., et al. 2000. *J. Pharmacol. Exp. Ther.* **293,** 281.

Angiogenesis: A Therapeutic Target for Cancer Therapy

Angiogenesis, a multi-step process, is essential for tumor growth and metastasis. Angiogenic growth factors such as bFGF, TNF-α, VEGF, and angiogenin promote angiogenesis by acting as autocrine or paracrine agents. Dormant tumors secrete inhibitory factors such as angiostatin, thrombospondins, and tissue inhibitors of metalloproteinases (TIMPs) that prevent tumors from switching to the angiogenic phenotype. Most tumors can remain 2 to 3 mm in size for years without any angiogenic activity. In this dormant stage, the rate of tumor cell proliferation is balanced by apoptosis of tumor cells. However, when they switch to the angiogenic phenotype they grow rapidly. The obligatory neovascularization is a rather uncommon process under normal conditions. Hence, angiogenesis has become a prominent target for therapeutic intervention in cancer patients.

Angiogenin Inhibitor (NCI-65828; N-65828)

A cell-permeable azo-naphthalene sulfonate compound that displays antitumor properties by selectively binding to the ribonucleolytic active site of angiogenin and inhibiting its activity (K_i = 81 µM). Delays the formation of tumors in athymic mice injected with PC-3 and HT-29 cells. *Purity: ≥95% by HPLC.*



Cat. No. 175610 10 mg $ 88

Ref.: Kao, R.Y., et al. 2002. *Proc. Natl. Acad. Sci. USA* **99,** 10066.

Mifepristone

A synthetic steroid that acts as a potent antagonist of progesterone and glucocorticoid receptors. Blocks P-glycoprotein (P-gp) function and P-gp-mediated drug resistance. Suppresses VEGF production and displays anti-angiogenic effects. *Purity: ≥98.5% by Titration.*

Cat. No. 475838 50 mg $ 52

Ref.: Sidell, N., et al. 2002. *Ann. N. Y. Acad. Sci.* **955,** 159; Hyder, S.M., et al. 2001. *Int. J. Cancer* **92,** 469; Sridhar, S., et al. 2001. *Cancer Res.* **61,** 7179; Greb, R.R., et al. 1997. *Hum. Reprod.* **12,** 1280; Gruol, D.J., et al. 1994. *Cancer Res.* **54,** 3088.

PlGF-1, Human, Recomb., *Spodoptera frugiperda*

A 131-amino acid splice variant of the human placenta growth factor (PlGF) gene. Antagonizes VEGF-induced angiogenesis and tumor growth by the formation of functionally inactive PlGF-1/VEGF heterodimers. *Purity: ≥90% by HPLC.*

Cat. No. 526610 5 µg $ 208

Ref.: Eriksson, A., et al. 2002. *Cancer Cell* **1,** 99; Khaliq, A., et al. 1999. *Lab. Invest.* **79,** 151; Ziche, M., et al. 1997. *Lab Invest.* **76,** 517; Birkenhager, R., et al. 1996. *Biochem. J.* **316,** 703.

PlGF-2, Human, Recomb., *Spodoptera frugiperda*

A 152-amino acid splice variant of the human placenta growth factor (PlGF) gene. In contrast to PlGF-1, it contains a highly basic 21 amino acid stretch at the C-terminal end. Has been shown to form a biologically active heterodimer with VEGF. *Purity: ≥80% by HPLC.*

Cat. No. 526612 5 µg $ 208

Ref.: Barillari, G., et al. 1998. *Am. J. Pathol.* **152,** 1161; Ziche, M. et al. 1997. *Lab Invest.* **76,** 517; Hauser, S., and Weich, H.A. 1993. *Growth Factors* **9,** 259.

TSRI265

A potent inhibitor of angiogenesis that blocks tumor growth *in vivo*. Binds to integrin $\alpha_v\beta_3$ and blocks its interaction with MMP-2. Has no direct effect on $\alpha_v\beta_3$ binding to vitronectin. *Purity: ≥95% by HPLC.*

Cat. No. 654100 1 mg $ 129

Ref.: Silletti, S., et al. 2001. *Proc. Natl. Acad. Sci. USA* **98,** 119.

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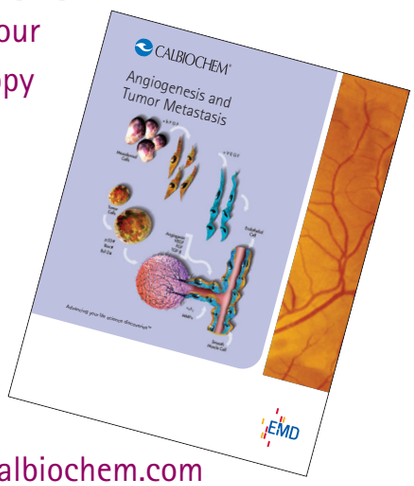

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Looking for Phospho-Specific Antibodies to Signaling Molecules?

Product	Cat. No.	Comments	Application*	Size	US $
Anti-FAK, Phospho-Specific (Tyr^{397}), Human (Rabbit)	341292	Recognizes the ~125 kDa FAK when phosphorylated at Tyr^{397}. This autophosphorylation site interacts with Src family SH2 and the p85 subunit of PI 3-Kinase.	IB, IH	10T	315
Anti-FAK, Phospho-Specific (Tyr^{576}), Human (Rabbit)	341294	Reacts with the ~125 kDa FAK phosphorylated at Tyr^{576}. This phosphorylation site is located within the catalytic domain of FAK and is phosphorylated by Src.	IB	10T	328
Anti-Lck, Phospho-Specific (Tyr^{505}), Human (Rabbit)	428100	Detects the 56 kDa Lck phosphorylated on Tyr^{505}. This phosphorylation negatively regulates Lck by maintaining it in an inactive conformation state.	IB	10T	345
Anti-ERK5, Phospho-Specific (Thr^{218}, Tyr^{220}), Human (Rabbit)	442688	Reacts with human ERK5 phosphorylated at Thr^{218} and Tyr^{220}. May also detect a truncated ERK5 protein at 30 - 35 kDa.	IB	10T	328
Anti-MAP Kinase ERK1/ERK2, Phospho-Specific (Thr^{202}/Tyr^{204}), Human (Rabbit)	442685	Detects the phosphorylated ERK1 and ERK2. Does not react with unphosphorylated proteins.	DB, IB	100 µl	263
Anti-MEK1/MEK2, Phospho-Specific (Ser$^{218/222}$), Human (Rabbit)	444955	Detects MEK1/MEK2 (~45 kDa) activated by Raf. May also detect a higher molecular weight band.	DB, IB	100 µl	325
Anti-p38 MAP Kinase, Phospho-Specific (Thr^{180}, Tyr^{182}), Human (Rabbit)	506119	Recognizes the dually phosphorylated p38 from several species. Reacts with endogenous active forms of p38α, β, and γ/ERK6 in a variety of cell types.	IB, IC	10T	315
Anti-MARCKS, Phospho-Specific (Ser$^{159, 163, 179}$), Mouse (Rabbit)	442709	Reacts with phosphorylated MARCKS in human, mouse, rabbit, and rat.	IB, IF	100 µl	295
Anti-MARCKS, Phospho-Specific (Ser$^{152/156}$), Rat (Rabbit)	442710	Immunogen used was a synthetic phosphopeptide corresponding to amino acids surrounding phosphorylated Ser^{152} and Ser^{156} of MARCKS.	DB, IB	100 µl	295
Anti-RON, Phospho-Specific (Tyr$^{1238/1239}$), Human (Rabbit)	557346	Reacts with human and mouse. Ron is activated by phosphorylation at Tyr$^{1238/1239}$.	IB	10T	355

*** DB:** dot blot; **IB:** immunoblotting; **IC:** immunocytochemistry; **IF:** immunofluorescence

NEW! Cell-Cycling Research Tools

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 antiproliferative and pro-apoptotic effects. *Purity: ≥95% by HPLC.*

Cat. No. 219457 1 mg $ 67

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

SB-218078

A potent and selective inhibitor of checkpoint kinase, Chk1, *in vitro*. Inhibits Chk1 phosphorylation of Cdc25C (IC_{50} = 15 nM). Acts as a weak inhibitor of Cdc2 (IC_{50} = 250 nM). *Purity: ≥90% by HPLC.*

Cat. No. 559402 1 mg $ 98

Ref.: Zhao, B., et al. 2002. *J. Biol. Chem.* **277**, 46609; Jackson, J.R., et al. 2000. *Cancer Res.* **60**, 566.

Also Available....

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

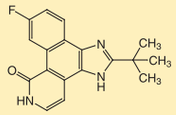
Cdk5 complexed with neuronal Cdc2-like kinase (Nclk). *Specific activity: ≥100,000 units/mg protein.*

Cat. No. 219459 250 units $ 252

JAK Inhibitor I

A potent inhibitor of Janus Protein Tyrosine Kinases (JAKs). Displays potent inhibitory activity against JAK1 (IC_{50} = 15 nM for murine JAK1), JAK2 (IC_{50} = 1 nM), JAK3 (K_i = 5 nM), and Tyk2 (IC_{50} = 1 nM). *Purity: ≥98% by HPLC.*

NEW!

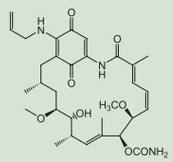


Cat. No. 420099 500 µg $ 77

Ref.: Thompson, J.E., et al. 2002. *Bioorg. Med. Chem. Lett.* **12**, 1219.

17-AAG

A potent synthetic derivative of Geldanamycin (Cat. No. 345805) that binds to Hsp90 (EC_{50} = 7.2 µM) and regulates its function. 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, blocks the Ras/Raf/MEK and PI 3-kinase signaling pathways. *Purity: ≥98% by HPLC.*

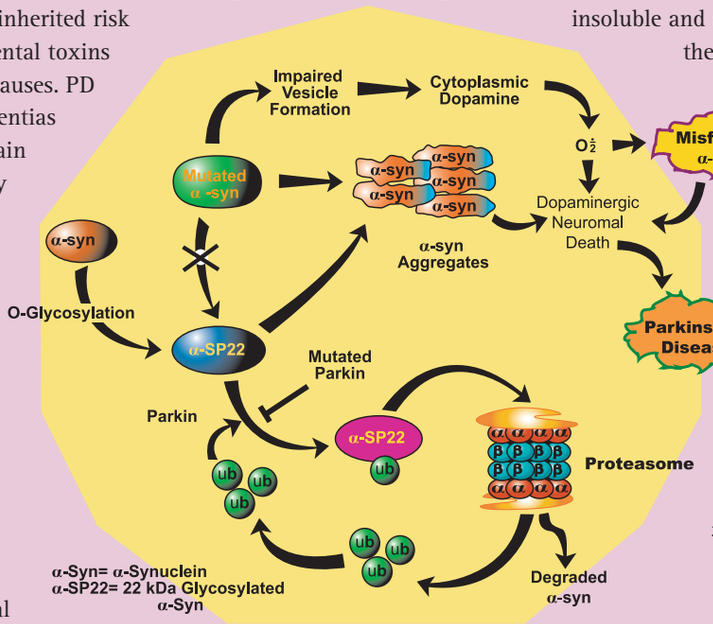


Cat. No. 100068 500 µg $ 165

Ref.: Basso, A.D., et al. 2002. *Oncogene* **21**, 1159; Schulte, T.W., and Neckers, L.M. 1998. *Cancer Chemother. Pharmacol.* **42**, 273; Schnur, R.C., et al. 1995. *J. Med. Chem.* **38**, 3806.

Parkinson's Disease: α-Synuclein, A Perpetrator of Disease

Parkinson's disease (PD), the second most common neurodegenerative disease, is a progressive neurological condition that affects substantia nigra (SN) in the midbrain region. The etiology of the disease is not completely understood, however, inherited risk factors and environmental toxins are considered likely causes. PD and certain other dementias are associated with brain lesions known as Lewy bodies, which contain α-synuclein (α-Syn) as the major component. Mutations in the α-Syn gene have been linked with certain familial forms of PD. It has been suggested that mutations in α-Syn (Ala^{53} to Thr^{53} and Ala^{30} to Pro^{30}) may cause a conformational change that renders α-Syn more prone to self-aggregation and deposition in Lewy bodies. Expression of mutant α-Syn in dopaminergic neurons impairs synaptic vesicle formation, increases cytoplasmic levels of dopamine, and increases superoxide radicals in the cytoplasm, which lead to oxidative stress and misfolding of α-Syn.



Various mutations in yet another gene, the Parkin gene, are reported in early autosomal-recessive form of PD, however, these mutations do not generate Lewy bodies. The Parkin gene's product is an E3 ubiquitin ligase. Known substrates of Parkin include Pael-R (Parkin-associated endothelin-receptor-like receptor), CDCrel-1 (cell-division-control-related protein 1), Synphilin-1, and a glycosylated form of α-Syn (α-SP22). Only the glycosylated form, α-SP22, is ubiquitinated by Parkin. Unfolding of Pael-R makes it insoluble and allows it to accumulate in the endoplasmic reticulum. Ubiquitination of Pael-R by Parkin leads to its degradation in the proteasome, however, failure to ubiquitinate it leads to the death of the neuron.

Ref.: Lotharius, J., and Brundin P. 2002. *Nat. Rev. Neurosci.* **3**, 932; Couzin, J. 2001. *Science* **294**, 1257; Haass, C., and Kahle, P.J. 2001. *Science* **293**, 224; McNaught, K.. et al. 2001. *Nat. Rev. Neurosci.* **2**, 589; Shimura, H. et al. 2001. *Science* **293**, 263.

Parkin Cleavage Inhibitor

(Ac-Leu-His-Thr-Asp-CHO)

A tetrapeptide aldehyde corresponding to the Parkin amino acid sequence 123 - 126 (putative scissile peptide bond Asp^{126} - Ser^{127}) that acts as an efficient inhibitor of apoptosis-associated parkin cleavage in SH-SY5Y and CHO cells. *Purity: ≥95% by HPLC.*

Cat. No. 512660 1 mg $ 60
5 mg $ 240

Ref.: Kahns, S., et al. 2002. *J. Biol. Chem.* **277**, 15303.

Antibodies for Parkinson's Disease Research

Product	Cat. No.	Comments	Application	Size	US $
Anti-Parkin, N-Terminal (83-97), Human (Goat)	512650	Immunogen used was a synthetic peptide corresponding to amino acids 83 - 97 of the human 65 kDa Parkin protein.	ELISA, IB, PS	100 µl	212
Anti-Parkin, Human (Rabbit)	PC372	Immunogen used was a synthetic peptide corresponding to amino acids 81 - 98 of human Parkin. Reacts with human, mouse, and rat.	FS, PS	25 µg	226
Anti-α-Synuclein (Ab-1), Rat (Guinea pig)	PC325	Immunogen used was a synthetic peptide corresponding to amino acids 123 - 140 of the C-terminus of the cloned rat α-synuclein. Reacts with bovine, human, mouse, and rat.	FS, IB, IF	50 µl	226
Anti-α-Synuclein, C-Terminal (116-131), Human (Goat)	575000	Immunogen used was a synthetic peptide corresponding to amino acids 116 - 131 of human α-synuclein.	ELISA, PS	100 µl	212

* **ELISA:** enzyme-linked immunosorbent assay; **FS:** frozen sections; **IB:** immunoblotting; **IF:** immunofluorescence; **IH:** immunohistochemistry; **IP:** immunoprecipitation; **PS:** paraffin sections

α-Synuclein, Human, Recomb., *E. coli*

An acidic neuronal protein of 140 amino acids that has been implicated in the pathogenesis of Parkinson's Disease and related neurodegenerative disorders. An important regulatory component of vesicular transport in neuronal cells. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 575001 200 µg $ 232

Ref.: Kim, J., et al. 1997. *Mo. Cells* **7**, 78; Paik, S.R. 1997. *Arch. Biochem. Biophys.* **344**, 325; Jakes, R., et al. 1994. *FEBS Lett.* **345**, 27.

α-Synuclein A30P, Human, Recomb., *E. coli*

A point mutant (A30P) of the α-synuclein gene that has been linked to autosomal dominant early onset Parkinson's Disease. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 575002 200 µg $ 295

Ref.: Park, S.M., et al. 2002. *Blood* **100**, 2506; Krüger, R., et al. 1998. *Nat. Genet.* **18**, 106.

α-Synuclein A53T, Human, Recomb., *E. coli*

A point mutant (A53T) of the α-synuclein gene that has been linked to autosomal dominant early onset Parkinson's Disease. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 575003 200 µg $ 295

Ref.: Park, S.M., et al. 2002. *Blood* **100**, 2506; Polymeropoulos, M.H., et al. 1997. *Science* **276**, 2045

α-Synuclein (ΔNAC), Human, Recomb., *E. coli*

A deletion mutant of the α-synuclein that lacks the non-Aβ component (NAC; amino acid residues 61-95). Does not bind to $A\beta_{1-38}$ whereas the precursor of the non-Aβ component of Alzheimer's disease amyloid (NACP) binds to $A\beta_{1-38}$. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 575004 100 µg $ 355

Ref.: Yoshimoto, M., et al. 1995. *Proc. Natl. Acad. Sci. USA* **92**, 9141; Ueda, K., et al. 1993. *Proc. Natl. Acad. Sci. USA* **90**, 11282.

α-Synuclein A30P/A53T, Human, Recomb., *E. coli*

A Parkinson's disease-related double mutant (A30P/A53T) of α-synuclein. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 575005 200 µg $ 295

Ref.: Park, S.M., et al. 2002. *Blood* **100**, 2506; Krüger, R., et al. 1998. *Nat. Genet.* **18**, 106; Polymeropoulos, M.H., et al. 1997. *Science* **276**, 2045.

α-Synuclein (61-140), Human, Recomb., *E. coli*

A deletion mutant of α-synuclein containing amino acid residues 61-140. *Purity: ≥95% by SDS-PAGE.*

Cat. No. 575006 100 µg $ 355

Ref.: Park, S.M., et al. 2002. *Blood* **100**, 2506; Park, S.M., et al. 2002. *Biochemistry* **41**, 4137.

α-Synuclein (96-140), Human, Recomb., *E. coli*

A deletion mutant of α-synuclein containing amino acid residues 96-140. *Purity: ≥95% by SDS-PAGE.*

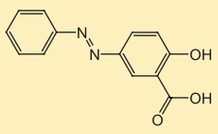
Cat. No. 575007 100 µg $ 355

Ref.: Park, S.M., et al. 2002. *Blood* **100**, 2506; Park, S.M., et al. 2002. *Biochemistry* **41**, 4137.

NEW! Tools for Alzheimer's Disease Research

Half Chrysamine G

A "half-molecule" of Chrysamine G that offers protection against $A\beta_{25-35}$ and $A\beta_{40}$-induced neuronal death (~ 0.1 - 1 µM). Shown to cross the blood-brain barrier. Exhibits minimal *in vivo* toxicity and displays low affinity to $A\beta_{40}$. *Purity: ≥97% by HPLC.*



Cat. No. 371977 1 mg $ 88

Ref.: Ishii, K., et al. 2002. *Neurosci. Lett.* **333**, 5.

NEW! Antibodies to Reelin

Anti-Reelin (40-189) (Mouse) (Clone 142)

In Western blots, shows three bands at ~400 - 450, 300, and 180 - 200 kDa. Recognizes reelin in a wide range of species. Useful for ELISA, IB, IF, IP, and IH.

Cat. No. 553730 100 µl $ 225

Anti-Reelin (164-496) (Mouse) (Clone G10)

In Western blot shows three bands at ~400 - 450, 300, and 180 - 200 kDa. Recognizes reelin in rodents. Useful for ELISA, FS, IB, IF, IP, and IH.

Cat. No. 553731 50 µl $ 232

Carmoxirole (EMD 45609, 2HCl)

A 5-carboxyindole-3-butylamine analog that acts as a selective, presynaptic dopamine D_2-receptor agonist. Inhibits adrenaline-induced platelet aggregation. *Purity: ≥98% by HPLC.*

Cat. No. 217510 5 mg $ 90

Ref.: Kirsten, R., et al. 1995. *Int. J. Clin. Pharmacol. Ther.* **33**, 76.

N-SMase Inhibitor, GW4869

A cell-permeable, potent inhibitor of neutral sphingomyelinase (IC_{50} = 1 µM for rat brain enzyme). Does not inhibit acid SMase. *Purity: ≥90% by HPLC.* Sold under license from GlaxoSmithKline.

Cat. No. 567715 1 mg $ 135

NEW! Antibodies for Alzheimer's Disease Research

Product	Cat. No.	Comments	Applications	Size	US $
Anti-β-Amyloid$_{40}$ (FCA3340), Human (Rabbit)	171608	Specifically recognizes Aβ$_{40}$ and p3-related fragments in human and canine. Does not cross-react with APP, Aβ$_{42}$ or Aβ$_{43}$.[1]	ELISA, IB, IF, IH, IP	50 µl	290
Anti-β-Amyloid$_{42}$ (FCA3542), Human (Rabbit)	171609	Specifically recognizes Aβ$_{42}$ and p3-related fragments in human and canine. Does not cross-react with APP, Aβ$_{40}$ or Aβ$_{43}$.[1]	ELISA, IB, IF, IH, IP	50 µl	290
Anti-β-Amyloid (Asp-1) (FCA18), Human (Rabbit)	PC729	Reacts with the first free aspartyl- residue and recognizes the N-terminus part of Aβ$_{1-x}$. Does not recognize -aspartyl- residues in full-length APP or N-acetylated aspartyl- or aspartyl-1 deleted Aβ peptides. Reacts with a variety of species.	IB, IP, PS	25 µl	190

Ref.: 1. Barelli, H., et al. 1997. *Mol. Med.* **3**, 695

* **EIA:** enzyme immunoassay; **ELISA:** enzyme-linked immunosorbent assay; **IB:** immunoblotting; **IF:** immunofluorescence; **IH:** immunohistochemistry; **IP:** immunoprecipitation; **PS:** paraffin sections

Aβ Fibrillogenesis Inhibitors

Aβ (β-amyloid peptide) is a major component of neuritic plaques and cerebrovascular amyloid deposits in the brains of patients with Alzheimer's disease (AD). A long-standing hypothesis has been that these fibrils are neurotoxic and are causative factors in the development and progression of AD. Hence, development of inhibitors of Aβ fibrillogenesis has become an important area of research. Calbiochem's Aβ Fibrillogenesis Inhibitors are pentapeptides that are selective inhibitors of Aβ formation and act as β-sheet breakers.

Product	Cat. No.	Comments	Size	US $
Aβ$_{40}$ Fibrillogenesis Inhibitor (Ac-K(Me)LV(Me)FF-NH$_2$)	171581	Cell-permeable pentapeptide based on the core domain of Aβ, which contains N-methyl amino acids in alternate positions. Displays stability towards denaturation and is resistant to chymotrypsin.[1,2]	1 mg 5 mg	72 273
Aβ$_{42}$ Fibrillogenesis Inhibitor I (LPFFD)	171586	Design is based on the central hydrophobic region in the N-terminal domain of Aβ. Binds to the monomeric/dimeric Aβ peptides with high affinity (K_d ~70 nM).[3,4]	5 mg	124
Aβ$_{42}$ Fibrillogenesis Inhibitor II (RVVIA-NH2)	171587	Contains the C-terminal sequence of Aβ$_{42}$ with Gly^{38} to Arg substitution, which results in improved solubility and potency.[5]	5 mg	124
Aβ$_{42}$ Fibrillogenesis Inhibitor III (Ac-LPFFD-NH2)	171588	A modified analog of Aβ$_{42}$ Fibrillogenesis Inhibitor I (Cat. No. 171586). Can cross the blood-brain barrier. Exhibits greater stability against proteolytic degradation.[6]	5 mg	124
γ-Secretase Inhibitor XVI	565777	A cell-permeable, potent inhibitor of γ-secretase (IC_{50} = 10 nM in 7PA2 cells) that prevents early Aβ oligomerization by blocking Aβ dimer and trimer formation.	5 mg	88

References:
1. Gordon, D.J., et al. 2002. *J. Peptide Res.* **60**, 37; 2. Gordon, D.J., et al. 2001. *Biochemistry* **40**, 8237; 3. Hetenyi, C., et al. 2002. *Bioorg. Med. Chem.* **10**, 1587; 4. Soto, C., et al. 1998. *Nat. Med.* **4**, 822; 5. Hetenyi, C., et al. 2002. *Biochem. Biophys. Res. Commun.* **292**, 931; 6. Permanne, B., et al. 2002. *FASEB J.* **16**, 860.

Kainic Acid, Natural

An excitatory amino acid receptor agonist selective for the kainate receptor subtype (K_i = 21 nM for ^{3}H-kainate binding in rat striatum). *Purity: ≥99% by HPLC.*

Cat. No. 420324 10 mg $ 145

Dihydrokainic Acid, Natural

A non-transportable inhibitor of L-glutamate uptake, selective to the Na$^+$-specific glutamate transporter GLT1 (EAAT2). *Purity: ≥99% by HPLC.*

Cat. No. 309810 10 mg $ 155

Ref.: Munoz, M.D., et al. 1987. *Neuropharmacology* **26**, 1.

βARK1 Inhibitor

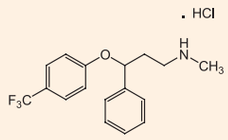
A selective inhibitor of βARK1 (β-adrenergic receptor kinase 1) (IC_{50} = 126 µM). *Purity: ≥95% by HPLC.*

Cat. No. 182200 5 mg $ 98

Ref.: Iino, M., et al. 2002. *J. Med. Chem.* **45**, 2150.

Fluoxetine, Hydrochloride

A cell-permeable, selective serotonin re-uptake inhibitor that regulates the phosphorylation of DARPP-32 and AMPA receptor. Reported to trigger oxidative stress-induced apoptotic cell death. *Purity: ≥98% by HPLC.*



Cat. No. 343290 25 mg $ 139

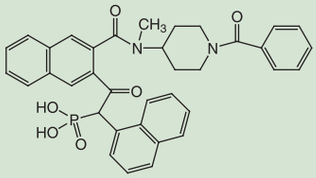
Ref.: Bartholoma, P., et al. 2002. *Biochem. Pharmacol.* **63**, 1507; Svenningsson, P., et al. 2002. *Proc. Natl. Acad. Sci. USA* **99**, 3182.

Neurochemical Corner

Cathepsin Inhibitors

Cathepsin G Inhibitor I

A potent, selective, reversible, and competitive inhibitor of cathepsin G (IC_{50} = 53 nM). Has only a trivial effect on chymotrypsin (K_i = 1.5 µM). *Purity: ≥98% by HPLC.*



Cat. No. 219372 1 mg $ 118

Ref.: Greco, M.N., et al. 2002. *J. Am. Chem. Soc.* **124**, 3810.

Cathepsin K Inhibitor I (Cbz-Leu-NH-CH_2-CO-CH_2-NH-Leu-Cbz)

A cell-permeable, symmetrical bis(acylamino)ketone that acts as a potent, selective, reversible inhibitor of cathepsin K ($K_{i,app}$ = 22 nM). Binds to cathepsin K and spans both the S- and S′-subsites. *Purity: ≥95% by HPLC.*

Cat. No. 219377 5 mg $ 124

Ref.: Claveau, D., et al. 2000. *Biochem. Pharmacol.* **60**, 759; Yamashita, D.S., et al. 1997. *J. Am. Chem. Soc.* **119**, 11351.

Cathepsin K Inhibitor II (Z-L-NHNHCONHNH-LF-Boc)

A cell-permeable peptidyl bis-carbohydrazide compound that acts as a potent, selective, reversible inhibitor of cathepsin K ($K_{i,app}$ = 6.0 nM). At higher concentrations, also inhibits cathepsin B and papain ($K_{i,app}$ = 510 nM, 1.2 µM, respectively). *Purity: ≥97% by HPLC.*

Cat. No. 219379 1 mg $ 88

Ref.: Wang, D., et al. 2002. *Biochemistry* **41**, 8849.

Cathepsin K Inhibitor III (Z-L-NHNHCONHNH-LF-NH_2)

A cell-permeable, potent, selective, reversible inhibitor of cathepsin K ($K_{i,app}$ = 9.7 nM). At higher concentrations, also inhibits the activities of cathepsin B, cathepsin L, and papain ($K_{i,app}$ = 5.1 µM, 120 nM, and 2.3 µM, respectively). *Purity: ≥97% by HPLC.*

Cat. No. 219381 1 mg $ 144

Ref.: Wang, D., et al. 2002. *Biochemistry* **41**, 8849.

Cathepsin L Inhibitor IV (1-Naphthalenesulfonyl-IW-CHO)

A potent inhibitor of cathepsin L (IC_{50} = 1.9 nM) that blocks the release of Ca^{2+} and hydroxyproline from bone and prevents bone loss in ovariectomized mice. *Purity: ≥98% by HPLC.*

Cat. No. 219433 1 mg $ 67

Ref.: Yasuma, T., et al. 1998. *J. Med. Chem.* **41**, 4301.

Cathepsin L Inhibitor V (Z-FY(OtBu)-COCHO)

A slow, tight-binding 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). *Purity: single spot by TLC.*

Cat. No. 219435 1 mg $ 78

Ref.: Lynas, J.F., et al. 2000. *Bioorg. Med. Chem. Lett.* **10**, 1771.

Add Convenience and Save Time... with Our New Cathepsin Assay Kits

- Sensitive Fluorogenic Detection Method
- Cresyl violet labeled substrates are used that generate red fluorescence upon cleavage
- Provided with a directional insert

Cathepsin B Detection Kit
Cat. No. 219346 1 kit $ 295

Cathepsin K Detection Kit
Cat. No. 219347 1 kit $ 295

Cathepsin L Detection Kit
Cat. No. 219348 1 kit $ 295

"It's only a conflict of interest if the data turns out good."

Nuclear Factor-κB: A Therapeutic Target in Inflammation

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

Stimulation of cells leads to the rapid phosphorylation, ubiquitination, and ultimate 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 target genes to induce their transcription of proinflammatory genes. NF-κB is highly activated at sites of inflammation in diverse diseases and can induce the transcription of proinflammatory cytokines, chemokines, adhesion molecules, MMPs, COX-2, and inducible nitric oxide (iNOS). Hence, NF-κB has been considered as a favorable target for therapy in various inflammatory diseases.

References
Ghosh, S., and Karin M. 2002. *Cell* **109**, S81; Delhase, M., et al. 1999. *Science* **284**, 309; Rahman, A., et al. 1999. *J. Immunol.* **162**, 5466; Miyazawa, K., et al. 1998. *Am. J. Pathol.* **152**, 793; Zandi, E., et al. 1998. *Science* **281**, 1360; Stancovski, I., and Baltimore, D. 1997. *Cell* **91**, 299; Baldwin, A.S. Jr. 1996. *Annu. Rev. Immunol.* **14**, 649.

NEW! NF-κB Related Research Tools

Product	Cat. No.	Comments	Size	US $
DHMEQ, Racemic	265660	A cell-permeable derivative of epoxyquinomicin C with anti-inflammatory and anti-tumor properties. Irreversibly inhibits TNF-α and TPA-induced NF-κB activation (~ 10 µg/ml in Jurkat cells) by blocking the nuclear translocation of p65. Does not inhibit IκB degradation.	1 mg	175
Isohelenin, *Inula* sp.	416157	A cell-permeable sesquiterpene lactone with anti-inflammatory properties. Irreversibly inhibits NF-κB activation by blocking the degradation of IκBα. Does not affect the DNA binding activity of activated NF-κB, or inhibit $p59^{fyn}$ and Src kinase activities.	1 mg	170
Kamebakaurin, *Isodon japonicus*	420340	A cell-permeable, potent, irreversible inhibitor of NF-κB activation. Targets DNA-binding activity of p50 and blocks the expression of anti-apoptotic NF-κB target genes. Does neither affect the induced degradation of IκB-α nor the translocation of NF-κB.	500 µg	134
Ro106-9920	557550	An anti-inflammatory agent that 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-1β and IL-6 inhibition) and rat.	1 mg 5 mg	67 232
Ro106-9920, Control	557551	An inactive control compound for Ro106-9920 (Cat. No. 557550) (IC_{50} > 80 µM)	1 mg	62
TIRAP Inhibitor Peptide, Cell-Permeable	613570	Toll-interleukin 1 receptor (TIR) domain-containing adapter protein. A cell-permeable synthetic peptide containing mouse $TIRAP_{138-151}$ fused to the *Drosophila* Antennapedia sequence. Specifically inhibits LPS-induced NF-κB activation and blocks IκBα degradation.	1 mg	191
TIRAP Inhibitor Peptide, Control, Cell-Permeable	613571	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	191

Also Available....

Flagellin, *Salmonella muenchen*

Stimulates the nuclear translocation of NF-κB and induces the release of both pro-inflammatory and anti-inflammatory mediators (IL-1, IL-6, IL-8, IL-10, IFN-γ, iNOS, TNF-α) *in vitro* and *in vivo*. Binds and activates Toll-like receptor 5 (TLR5), and activates interleukin-1 receptor-associated kinase (IRAK). *Purity: >95% by SDS-PAGE.*

Cat. No. 341820 100 µg $ 285

Pam_3Cys-Ser-$(Lys)_4$, Hydrochloride

A cell-permeable, cationic lipohexapeptide analog that activates monocytes and macrophages and induces the release of IL-1, IL-6, TNF-α, superoxide, and NO. Promotes the nuclear translocation of NF-κB. Also reported to enhance tyrosine protein phosphorylation and activation of ERK1/2 and MEK1/2. *Purity: >90% by HPLC.*

Cat. No. 506350 2 mg $ 175

NEW! Tools for Apoptosis Research: Granzymes

Granzymes, a family of serine proteases, are released from cytoplasmic granules of cytotoxic lymphocytes (CTLs) and Natural Killer (NK) cells. They enter the target cell via an endocytotic process and induce apoptosis. Granzyme B is the most powerful pro-apoptotic member of this family. It can trigger apoptosis directly through the activation of caspases or indirectly via mitochondrial release of cytochrome c and activation of apoptosome. Granzyme A appears to target the SET complex, resulting in single-stranded DNA breaks.

Granzyme A, Human, Recombinant, *E. coli.*
Cat. No. 368044 10 µg $ 285

Granzyme B, Human, Recombinant, *E. coli.*
Cat. No. 368043 10 µg $ 285

Granzyme K, Human, Recombinant, *E. coli.*
Cat. No. 368046 10 µg $ 285

NEW! Substrates for Caspases

Caspase-1 Substrate XV, Cell-Permeable, Fluorogenic (N$^{\alpha}$-5-Tetramethylrhodaminyl-YVADAC(*S*-acrylodan)-OH
A cell-permeable, internally-quenched fluorogenic peptide substrate for detecting caspase-1-like protease activity in living cells or tissues. Cleavage occurs between Asp and Ala residues ($k_{cat}/K_m \sim 8.5 \times 10^{-2}$ $\mu M^{-1}s^{-1}$) resulting in an increase in fluorescence. *Purity: ≥90% by HPLC.*

Cat. No. 218828 500 µg $ 149

Ref.: Nishii, W., et al. 2002. *FEBS Lett.* **518**, 149.

Caspase-3 Substrate IX, Fluorogenic (Z-DEVD)$_2$-Rh 110)
A non-fluorescent peptidyl (DEVD)-Rhodamine 110-bisamide that acts as a highly sensitive, photostable caspase-3 fluorogenic substrate. Can detect less than 1 ng/ml of caspase-3. Useful for high throughput screening applications. *Purity: ≥95% by HPLC.*

Cat. No. 218829 1 mg $ 139

Ref.: Hug, H., et al. 1999. *Biochemistry* **38**, 13906; Liu, J., et al. 1999. *Bioorg. Med. Chem. Lett.* **9**, 3231.

Omi/htrA2 Protease Inhibitor
A cell-permeable furfurylidine-thiobarbituric acid-based compound that acts as a potent, selective, competitive, and reversible inhibitor of the pro-apoptotic, heat-inducible, mitochondrial serine protease Omi/htrA2 (IC_{50} = 9.5 µM for His-Omi134-458). Does not affect other serine proteases.

Cat. No. 496150 10 mg $ 90

Ref.: Cilenti, L., et al. 2003. *J. Biol. Chem.* **278**, 11489.

NEW! Potent Caspase Inhibitor Q-VD-OPh (N-(2-Quinolyl)valyl-O-methylaspartyl-(2,6-difluorophenoxy)methyl Ketone)
A highly potent, irreversible caspase-selective inhibitor (IC_{50} = 25 nM, 50 nM, 100 nM, and 430 nM for caspase-3,-1,-8, and -9, respectively) that can cross the blood-brain barrier. Protects neurotoxin-insulted neurons from apoptotic death. *Purity: ≥95% by HPLC.*

Cat. No. 551475 1 mg $ 134

NEW! Calpain Assay Kits

Calpain 1 ELISA Kit
Sensitivity: ≤0.3 ng/ml; Assay Time: 3.5 hours; Sample Type: Plasma, serum, cells, and tissue extracts.
Provided with an antibody-coated microplate, calpain 1 standard, detector antibody, HRP-conjugated antibody, TMB substrate, assay diluent, CytoBuster™ protein extraction reagent, wash buffer concentrate, stop solution, plate sealer, and a directional insert.

Cat. No. QIA118 1 Kit $ 464

Calpain Activity Assay Kit, Fluorogenic
Assay Time: 1.5 hours; Sample Type: Cell lysates, plasma, serum.
Provided with a calibration standard, calpain 1 positive control, substrate, activation buffer, inhibition buffer, reduction agent, assay buffer, cell lysis buffer, microtiter plate, plate sealer, and a directional insert. Requires a fluorimeter or a microplate reader (Ex. max: ~360 nm; Em. max: ~460 nm).

Cat. No. QIA120 1 Kit $ 345

NEW! Antibodies for Osteoporosis Related Research

Product	Cat. No.	Comments	Application*	Size	US $
Anti-Osteocalcin (1-22), Human (Rabbit)	499055	Reacts with human osteocalcin 1 - 22, 1 - 44, and 1 - 49. Does not react with bovine and sheep osteocalcin.	IB, RIA	100 µl	241
Anti-Osteonectin, Human (Rabbit)	499255	Recognizes the 43 kDa noncollagenous osteonectin found in the extracellular matrix of human bone. Does not react with osteopontin and bone sialoprotein.	ELISA, IB, PS.	100 µl	241
Anti-Osteopontin (75-90), Human (Rabbit)	499265	Specifically recognizes human osteopontin.	ELISA, IB, IH	100 µl	232
Anti-Osteostatin (107-111), Human (Rabbit)	499280	Reacts with human osteostatin. Reactivity with other PTHrP fragments has not been determined.	ELISA	100 µl	241
Anti-Bone Sialoprotein, Human (Chicken)	203635	Recognizes the 70 - 80 kDa human bone sialoprotein from osteoblasts and osteocytes. Does not cross-react with osteocalcin, osteonectin, osteopontin, or bone alkaline phosphatase.	IB, IH, RIA	100 µl	232
Anti-Bone Sialoprotein, Human (Mouse)	203637	Recognizes the 70 - 80 kDa human bone sialoprotein from osteoblasts and osteocytes. Does not cross-react with osteocalcin, osteonectin, osteopontin, or bone alkaline phosphatase.	ELISA, IB, PS	100 µg	241

* **ELISA:** enzyme-linked immunosorbent assay; **FS:** frozen sections; **IB:** immunoblotting; **IF:** immunofluorescence; **IH:** immunohistochemistry; **IP:** immunoprecipitation; **PS:** paraffin sections

Studying G-Protein-Related Phenomenon?

G-Protein, $\beta_1\gamma_2$-Subunit, Rat, Recomb.

Active G-protein $\beta_1\gamma_2$ dimers purified from doubly infected *Spodoptera frugiperda* cells. The γ_2-subunit contains a His•Tag®. Suitable for use in reconstitution experiments. *Purity: ≥90% by SDS-PAGE.*

Cat. No. 371777 5 µg $ 395

Ref.: Kozasa, T. and Gilman, A.G. 1995. *J. Biol. Chem.* **270**,1734.

$G_i\alpha$-1/$G_q\alpha$-Subunit Chimera, Rat, Recomb.

A soluble, functional chimeric G-protein expressed in *Spodoptera frugiperda*. Comprised of $G_i\alpha$-1 sequences substituted with sufficient $G_q\alpha$ sequences to allow functional coupling with receptors normally coupled with G_q and to inhibit coupling with receptors normally coupled with G_i. *Purity: ≥80% by SDS-PAGE.*

Cat. No. 371797 10 µg $ 245

REP-1, His•Tag®, Rat, Recomb., *Spodoptera frugiperda*

A molecular chaperone that binds to Rab proteins stoichiometrically and promotes the catalytic activity of GGTase-II. *Purity: ≥90% by SDS-PAGE.*

Cat. No. 554000 50 µg $ 209

Ref.: Alexandrov, K., et al. 1998. *FEBS Lett.* **425**, 460; Casey, P.J., and Seabra, M.C. 1996. *J. Biol. Chem.* **271**, 5289.

REP-2, His•Tag®, Human, Recomb., *Spodoptera frugiperda*

Binds to a wide range of Rab GGTases with high affinity and supports the prenylation of Rab GTPase mediated by Rab GGTase (with the exception of Rab27). *Purity: ≥90% by SDS-PAGE.*

Cat. No. 554005 50 µg $ 195

Ref.: Chan, D., et al. 2000. *J. Cell Physiol.* **185**, 339; Seabra, M.C., et al. 1995. *J. Biol. Chem.* **270**, 24420.

NEW! Inhibitor of 20S Proteasome Activity
α-Methylomuralide

A cell-permeable α-methyl analog of *clasto*-Lactacystin β-Lactone (Cat. No. 426102) with improved hydrolytic stability. A potent, selective, irreversible inhibitor of proteasome function. *Purity: ≥95% by TLC.*

Cat. No. 426104 100 µg $ 185

Ref.: Corey, E.J., and Li. W-D.Z. 1998. *Tetrahedron Lett.* **39**, 7475.

Estren (4-Estren-3α,17β-diol)

A steroid ligand with lower binding affinity for the estrogen receptor. Does not stimulate any transcriptional activity. Shown to attenuate osteoblast apoptosis and stimulate osteoclast apoptosis. Increases bone mass and strength without affecting reproductive organs.

Cat. No. 330160 10 mg $ 196

Ref.: Kousteni, S., et al. 2002. *Science* **298**, 843.

Ergtoxin, *Centruroides noxius*, Recomb., *E. coli.*

Specifically blocks the ERG (ether-a-go-go-related) K^+ channels in a variety of tissues and species. *Purity: ≥98% by HPLC.*

Cat. No. 324940 10 µg $ 115

Ref.: Bottiglieri, C., et al. 2000. *FEBS Lett.* **479**, 155; Gurrola, G.B., et al. 1999. *FASEB J.* **13**, 963.

Looking for Better Tools for Proteomics Research? ... Check out our New ProteoExtract™ Kits

Our newly developed ProteoExtract™ Kits are designed for fast and reproducible extraction of proteins from a wide variety of samples, including bacteria, yeast, and mammalian cells or tissues. Each kit includes proteomics grade ultra-pure chemicals for optimal resolution and reproducibility in 2D-gel electrophoresis. In order to reduce sample viscosity and increase spot resolution, Benzonase®, a non-specific nuclease, is included with each kit.

Ref.: Yuan, X., et al. 2002. *Electrophoresis* **23**, 1185.

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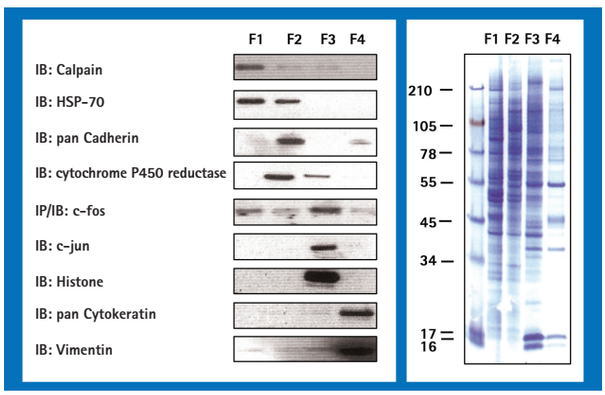

Fig. 3: SDS-PAGE and immunoblotting of selected marker proteins demonstrate a separation efficiency >90% of subcellular compartments of mammalian tissue cultured cells using S-PEK Kit.

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Cat. No. 182730 1 g $ 85 5 g $ 290

Ref.: Henningsen, R., et al. 2002. *Proteomics* **2**, 1479; Santoni, V., et al. 2000. *Electrophoresis* **21**, 3329.

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