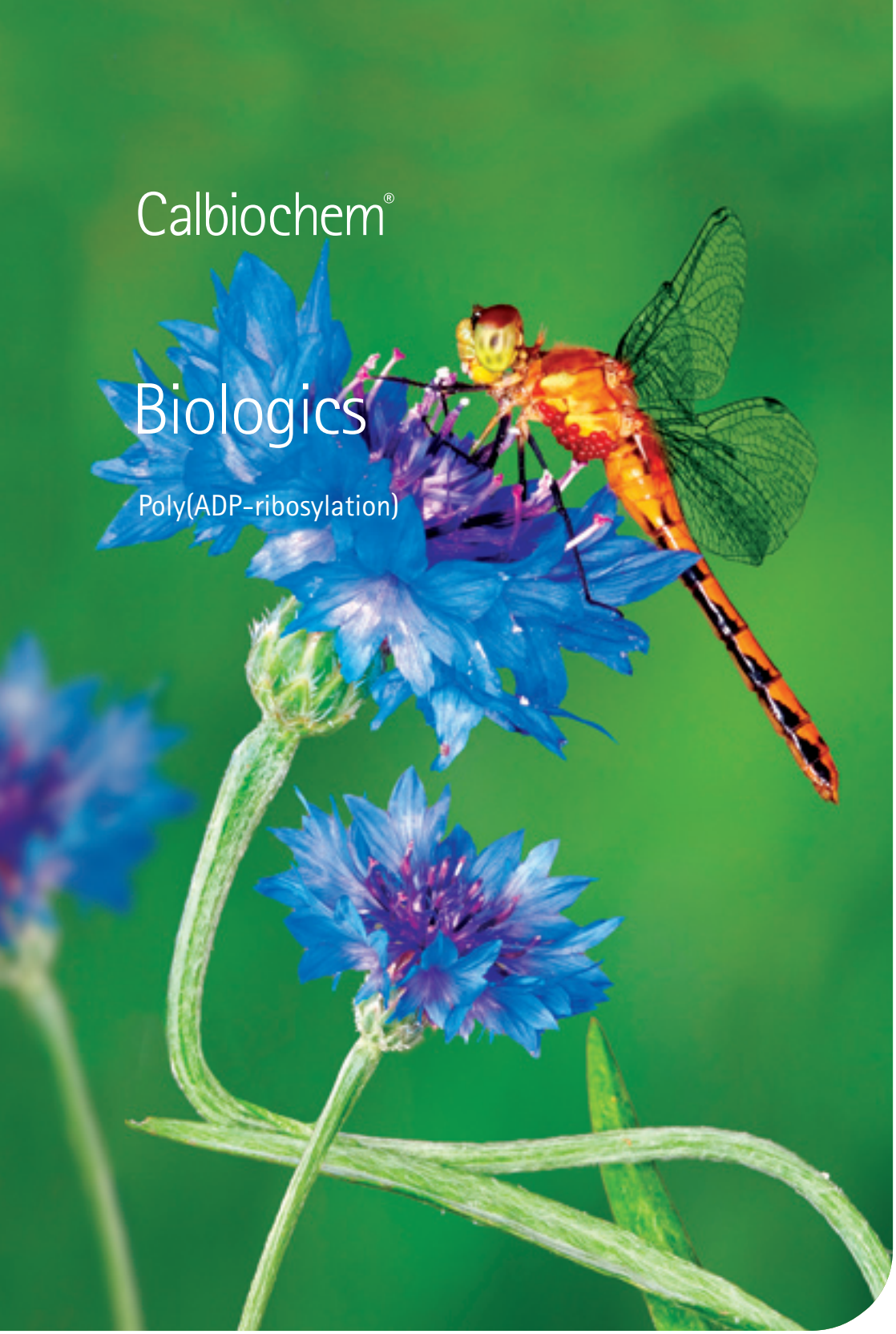

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Biologics

Poly(ADP-ribosylation)

Volume 33, No. 1, 2007

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Poly(ADP-ribosylation)

PARP in DNA Repair and Apoptosis

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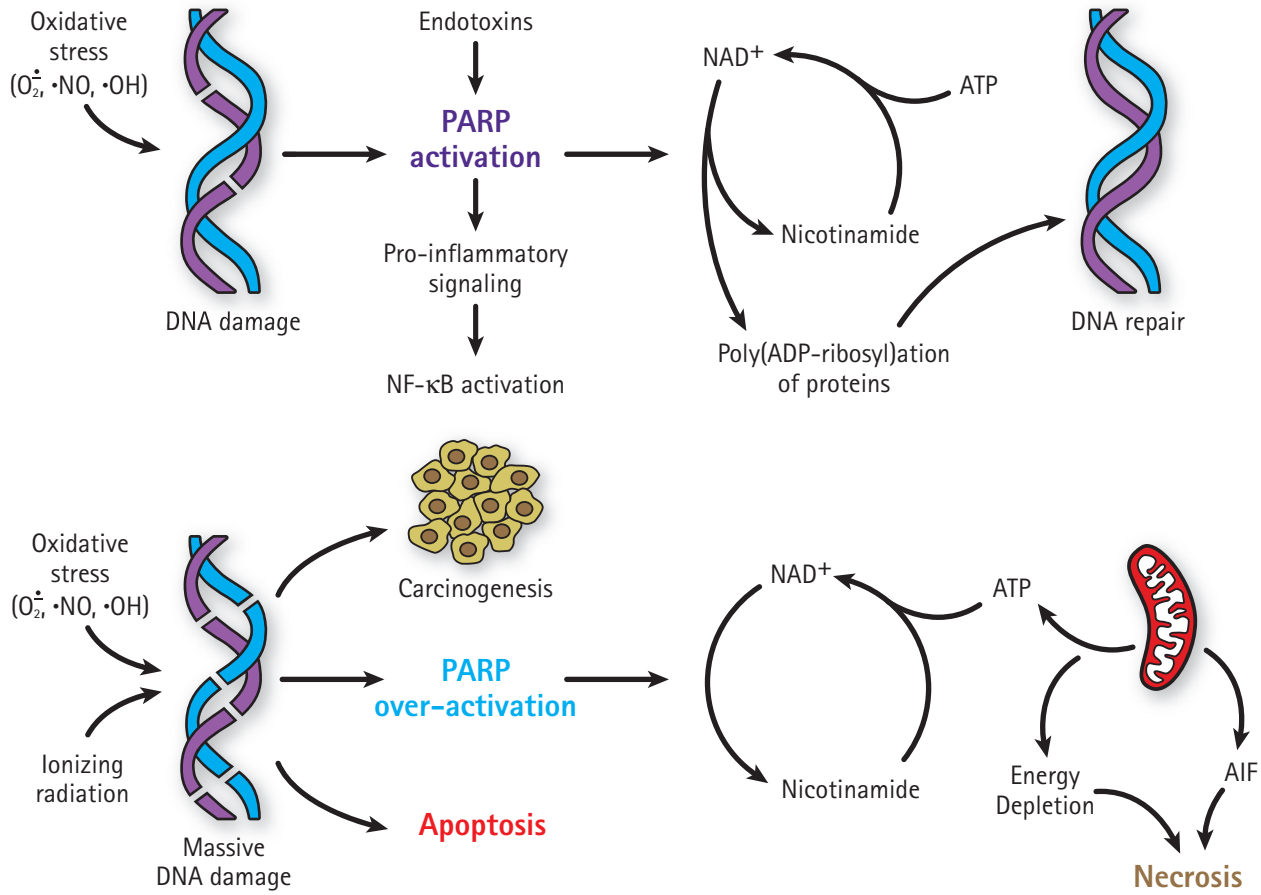
Poly(ADP-ribosyl)ation (pADPr), a covalent post-translational modification process that occurs during DNA repair, replication and transcription, is brought about by poly(ADP-ribose)polymerase (PARP), which is activated by breaks in DNA strands. PARPs are a group of Zn^{2+} -binding enzymes that catalyze the transfer of ADP-ribose (ADPr) units from NAD^+ to protein acceptors to produce linear and/or branched polymers of ADPr. PARP activity has been reported in all eukaryotes except yeast. The 'classical' 113 kDa type I PARP is an abundant protein and is the major contributor of the poly(ADP-ribosyl)ating activity in higher eukaryotes. It has become a major target for drug design for the treatment of cancer, diabetes, inflammation, retroviral infection, and other diseases. Type II PARP is smaller than the classical zinc-finger-containing PARP and is believed to participate in DNA repair during apoptosis. Type III PARP is a large protein containing ankyrin repeats and a PARP catalytic domain and the only known member of this subgroup is tankyrase. Human tankyrase is localized at telomeres in living cells, and is reported to be involved in the regulation of telomeric function. Most of the physiological substrates of poly(ADP-ribosyl)ation reactions are nuclear proteins, including those that are involved in the metabolism of nucleic acids and in the maintenance of chromatin architecture.

PARP is a multifunctional enzyme consisting of three domains: a DNA-binding domain (DBD), an automodification domain, and a catalytic domain. The DBD, a 42 kDa N-terminal region, extends from the initiator Met to Thr^{373} in human PARP. It contains two zinc fingers and two helix–turn–helix motifs and is rich in basic residues, which are involved in the interaction of the enzyme with DNA. Zinc finger 1 (F1) occupies the region between Cys^{21} and Cys^{56}, while zinc finger 2 (F2) is found between Cys^{125} and Cys^{162}. The automodification domain is located in the central region of the enzyme and resides between Ala^{374} and Leu^{525} in human PARP. This domain contains the majority of the glutamic acid residues that are involved in PARP automodification. In addition, the automodification domain contains a BRCT (BRCA1 C-terminus) domain that lies between Ala^{384} and Ser^{479} and consists of about 95 amino acids found in several proteins that regulate cell-cycle checkpoints and DNA repair. BRCT domains are protein-protein interaction modules that allow BRCT-motif-containing proteins to establish strong and specific associations. The catalytic domain, a 55 kDa segment, is located in the C-terminal region of the enzyme and spans from residues Thr^{526} to Trp^{1014} in human PARP. The catalytic activity of this fragment is not stimulated by DNA strand breaks, and it corresponds only to the basal activity of the native enzyme. The ADPr transferase activity has been confined to a 40 kDa region at the extreme C-terminus of the enzyme, which is referred to as the minimal catalytic domain. This region can catalyze the initiation, elongation, and branching of ADPr polymers independently of the presence of DNA. The loss of the last 45 amino acids at the C-terminal end of this domain completely abolishes enzyme activity. Residues spanning positions Leu^{859} to Tyr^{908} in human PARP are well conserved and comprise the 'PARP signature' sequence.

The extent of poly(ADP-ribosyl)ation is an important determinant of NAD^+ levels in cells. Upon binding to DNA breaks, activated PARP cleaves NAD^+ into nicotinamide and ADP-ribose. The ADP-ribose then polymerizes onto nuclear acceptor proteins including histones, transcription factors, and PARP itself. In normal, undamaged cells, NAD^+ levels range from 400 to 500 µM. However, PARP activation following DNA damage by radiation or cytotoxic agents reduces



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

DNA damage, the single most important factor in the regulation of poly(ADP-ribosyl)ation reactions, can stimulate the catalytic activity of PARP by about 500 fold. PARP is required for repair of single strand breaks and base excision repair. Inhibition of PARP is shown to reduce DNA repair, increase the cytotoxicity of DNA-damaging agents, cause telomere shortening, and enhance apoptosis. The cytotoxicity of PARP inhibitors is due to an increase in the half-life of DNA strand breaks, which increases genomic instability. PARP cleavage by caspase-3 is considered as an early event in apoptotic cell death. PARP degradation has also been reported during necrosis, although believed to be through a different process. In necrosis, PARP is cleaved into two major fragments of 89 and 50 kDa, and two minor fragments of 35 and 40 kDa. However, during apoptosis PARP is cleaved into only two fragments of 89 kDa and 24 kDa.

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Antibodies for DNA Damage and Repair Research

Name	Cat. No.	Comments	Size	Price
Anti-ATM (Ab-1) (13-24) Rabbit pAb	PC85	Liquid, purified. Immunogen used was a synthetic peptide corresponding to amino acids 13-24 of human ATM. Recognizes the ~350 kDa ATM protein in Daudi, HeLa, and AT169a cells. **IB**	100 µg	€277
Anti-ATM (Ab-2) Mouse mAb (6B7)	OP90	Liquid, purified. Immunogen used was a synthetic peptide corresponding to amino acids 368-380 of human ATM. Recognizes the ~350 kDa ATM protein in Daudi and HeLa cells. **IP**	200 µg	€294
Anti-ATM (Ab-3) (819-844) Rabbit pAb	PC116	Liquid, purified. Immunogen used was a synthetic peptide corresponding to amino acids 819-844 of human ATM. Recognizes the ~350 kDa ATM protein in Daudi and HeLa cells. **IB, IP**	100 µg	€277
Anti-ATR (Ab-2) (2122-2644) Rabbit pAb	PC538	Undiluted serum. Immunogen used was a synthetic peptide corresponding to amino acids 2122-2644 of human ATR. Recognizes the ~300 kDa ATR protein in hamster, human, and mouse testis tissue extracts. **IB**	50 µl	€294
Anti-PARP (215-228) Rabbit pAb	512739	Undiluted serum. Immunogen used was a synthetic peptide corresponding to amino acids 215-228 of human PARP. Recognizes the ~110-116 kDa full length PARP and its ~85 kDa cleaved fragment. **ELISA, IB, IF**	100 µl	€331
Anti-PARP-1 (197-214) Rabbit pAb	512738	Undiluted serum. Immunogen used was a synthetic peptide corresponding to amino acids 197-214 of human PARP. Recognizes the ~116 kDa full-length PARP and its ~29 kDa cleaved fragment. **ELISA, IB, IC, IF, IP**	100 µl	€304
Anti-PARP-1 (Ab-1) Rabbit pAb	PC100	Liquid, purifed. Immunogen used was a synthetic peptide from the N-terminus of human PARP. Recognizes the ~116 kDa full-length PARP protein and its ~24 kDa cleaved fragment in etopside-treated HL-60 cells. **IB**	100 µg	€277
Anti-PARP-1 (Ab-2) Mouse mAb (C-2-10)	AM30	Liquid, purified. Immunogen used was purified PARP from calf thymus. Recognizes the ~116 kDa full-length PARP and its ~85 kDa cleaved fragment in etopside-treated HL-60 cells. Exhibits cross-reactivity with hamster, human, monkey, mouse, and rat. **IB, IF**	100 µg	€294
Anti-PARP-1 (Ab-3) Mouse mAb (F1-23)	AM68	Undiluted ascites. Immunogen used was purified PARP from calf thymus. Recognizes the ~116 kDa full-length and the ~24 kDa cleaved PARP in etopside-treated HL-60 cells. Exhibits cross-reactivity with bovine and human. **ELISA, IB, IF, IP**	25 µl	€216
Anti-PARP-1 Automodification Domain (509-524) Rabbit pAb	512737	Undiluted serum. Immunogen used was a synthetic peptide corresponding to amino acids 509-524 of bovine PARP automodification domain. Recognizes the ~116 kDa full-length PARP protein and the ~85 kDa cleaved fragment of PARP. Exhibits cross-reactivity with bovine, hamster, human, monkey, mouse, and rat. **ELISA, IB, IP**	100 µl	€305
Anti-PARP-1 Rabbit pAb	512734	Undiluted serum. Immunogen used was bovine PARP-1. Recognizes the ~110-116 kDa full length PARP in bovine, gerbil, human, monkey, mouse, and rat. **ELISA, IB, IC, IP, NT**	100 µl	€305
Anti-SMG1 Rabbit pAb	DR1035	Liquid, immunoaffinity purified. Immunogen used was a synthetic peptide corresponding to amino acids near the C-terminus of human SMG1. Recognizes the ~340 kDa SMG protein in HeLa cell nuclear extracts. **IB**	50 µg	€130

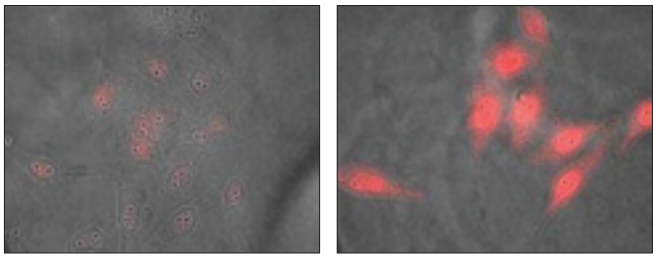
ELISA: enzyme-linked immunosorbent assay; **IB**: immunoblotting; **IC**: immunocytochemistry; **IF**: immunofluorescence; **IP**: immunoprecipitation

PhosphoDetect™ Anti-ATM (pSer^{1981}) Mouse mAb (10H11.E12)

Liquid, Protein G purified. Immunogen used was a synthetic phosphopeptide corresponding to amino acids 1974-1988 surrounding the Ser^{1981} phosphorylation site of human ATM. Recognizes the ~370 kDa ATM protein phosphorylated on Ser^{1981} in camptothecin-treated HeLa cells. Suitable for immunoblotting and immunocytochemistry.

Sold under license of U.S. Patent 7,108,992.

Cat. No. DR1002 **50 µg** **€148**



HeLa cells | HeLa cells + camptothecin

Detection of human ATM phosphorylated at (Ser^{1981}) by immunofluorescence. Samples: Untreated (left panel) and camptothecin-treated (10 µM, 2 h) HeLa cells, fixed with 100% methanol (right panel). Primary antibody: PhosphoDetect™ Anti-ATM (pSer^{1981}) Mouse mAb (10H11.E12) (Cat. No. DR1002) (1.5 µg/ml).

Antibodies for DNA Damage and Repair Research *(continued...)*

Anti-DDB1 (1128-1140) Goat pAb

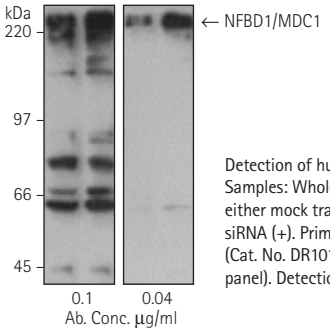
Liquid, immunoaffinity purified. Immunogen used was a synthetic peptide corresponding to amino acids 1128-1140 of human DDB1. Recognizes the ~127 kDa DDB1 protein. Exhibits reactivity with human and mouse. Suitable for immunoblotting.

Cat. No. PC718 **100 µg** **€345**

Anti-NFBD1/MDC1 Rabbit pAb

Liquid, immunoaffinity purified. Immunogen used was a synthetic peptide corresponding to amino acids encoded by exon 10 of human NFBD1/MDC1. Recognizes the ~250 kDa NFBD1/MDC1 protein in HeLa cells. Suitable for immunoblotting and immunoprecipitation.

Cat. No. DR1018 **100 µg** **€313**



Detection of human NFBD1/MDC1 by immunoblotting. Samples: Whole cell lysate (50 µg) from HEK293 cells, either mock transfected (-) or transfected with NFBD1/MDC siRNA (+). Primary antibody: Anti-NFBD1/MDC1 Rabbit pAb (Cat. No. DR1018) (0.1 µg/ml, left panel or 0.04 µg/ml, right panel). Detection: chemiluminescence.

PARP, Bovine Thymus

A full-length Poly(ADP-ribose) polymerase (PARP) purified from bovine thymus using DNA-cellulose affinity chromatography. *Specific activity: ≥200 nmol ADP-ribose/min/mg protein.* M.W. 116,000

Cat. No. 124025 **100 µg** **€265**

Also available...

PARP Cleavage Detection Kit

Designed to detect poly(ADP-ribose) polymerase (PARP) cleavage by immunoblotting. Each kit is provided with a highly specific rabbit polyclonal antibody that detects 116 kDa PARP and the 85 kDa apoptosis-related cleavage fragment from human, bovine, rat, and mouse.

Cat. No. 512729 **1 kit** **€325**

Poly(ADP-ribose) polymerase Inhibitors

PARP Inhibitor I, 3-ABA

(3-Aminobenzamide)

A cell-permeable inhibitor of PARP (K_i = 500 nM). Has minimal effect on bacterial toxin-mediated ADP-ribosylation. An inhibitor of UV-induced apoptosis. *Purity: ≥97% by TLC.* M.W. 136.2

Cat. No. 165350 **100 mg** **€37**

Ref.: De Soto, J.A. and Deng, C-X. 2006. *Int. J. Med. Sci.* **3,** 117.

PARP Inhibitor II, INH_2BP

(5-Iodo-6-amino-1,2-benzopyrone)

A cell-permeable PARP inhibitor. Offers protection against peroxynitrite and hydroxyl radicals *in vitro* and *in vivo* and abrogates peroxynitrite-induced mitochondrial transmembrane potential ($\Delta\Psi_m$) reduction. *Purity: ≥98% by HPLC.* M.W. 287.1

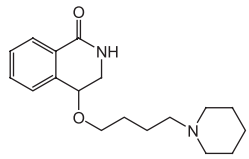
Cat. No. 407850 **5 mg** **€61**

Ref.: Cole, G.A., et al. 1991. *Biochem Biophys. Res. Commun.* **180,** 504.

PARP Inhibitor III, DPQ

(3,4-Dihydro-5[4-(1-piperindinyl)butoxy]-1(2H)-isoquinoline)

A potent and selective PARP inhibitor (IC_{50} = 40 nM). *Purity: ≥90% by HPLC.* M.W. 302.4



Cat. No. 300270 **1 mg** **€87**

Ref.: Eliasson, M.J., et al. 1997. *Nat. Med.* **3,** 1089; Suto, M.J., et al. 1991. *Anticancer Drug Des.* **6,** 107

Poly(ADP-ribose) polymerase Inhibitors *(continued...)*

PARP Inhibitor IV, IQD

(1,5-Dihydroxyisoquinoline)

A potent, cell-permeable PARP inhibitor (IC_{50} = 390 nM). *Purity: ≥98% by TLC.* M.W. 161.2

Cat. No. 419800 **5 mg** **€61**

Ref.: Dalamu, M., et al. 1996. *Exp. Cell Res.* **228,** 14; Zhang, J., et al. 1994. *Science* **263,** 687; Banasik, M., et al. 1992. *J. Biol. Chem.* **267,** 1569.

PARP Inhibitor V, 4-ANI

(4-Amino-1,8-naphthalimide)

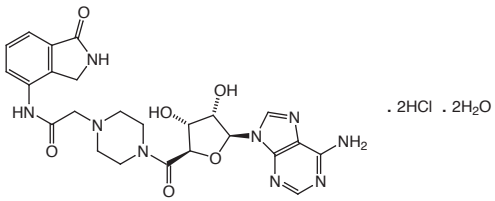
A potent, cell-permeable inhibitor of PARP (IC_{50}= 180 nM *in vitro*). *Purity: ≥95% by HPLC.* M.W. 212.2

Cat. No. 164585 **100 mg** **€61**

Ref.: Bowes, J., and Thiemermann, C. 1998. *Br. J. Pharmacol.* **124,** 1254; Thiememann, C., et al. 1997. *Proc. Natl. Acad. Sci. USA* **94,** 679; Radons, J., et al. 1996. *Biochem. Biophys. Res. Commun.* **199,** 1270; Banasik, M., et al. 1992. *J. Biol. Chem.* **267,** 1569.

PARP Inhibitor IX, EB-47

A cell-permeable, adenosine-substituted, isoindolinone compound that acts as a potent inhibitor of PARP-1 IC_{50} = 45 nM). *Purity: ≥95% by HPLC.* M.W. 646.5



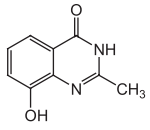
Cat. No. 324473 **1 mg** **€76**

Ref.: Jagtap, P.G., et al. 2004. *Bioorg. Med. Chem. Lett.* **14,** 81.

PARP Inhibitor VI, NU1025

(8-Hydroxy-2-methylquinazoline-4-one)

A cell-permeable, potent inhibitor of PARP-1 (IC_{50} = 400 nM). *Purity: ≥98% by HPLC.* M.W. 176.2

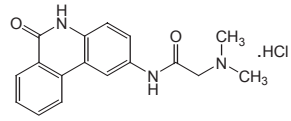


Cat. No. 493800 **5 mg** **€131**

Ref.: Delaney, C.A., et al. 2000. *Clin. Cancer Res.* **6,** 2860; Bowman, K.J., et al. 1998. *Br. J. Cancer* **78,** 1269; Griffin, R.J., et al. 1998. *J. Med. Chem.* **41,** 5247; Boulton, S., et al. 1995. *Br. J. Cancer* **72,** 849; Griffin, R.J., et al. 1995. *Anticancer Drug Res.* **10,** 507.

PARP Inhibitor VIII, PJ34

A cell-permeable, water-soluble phenanthridinone-derivative that acts as a potent inhibitor of PARP (EC_{50} = 20 nM). Exhibits about 10,000 times greater potency than 3-Aminobenzamide (Cat. No. 165350; EC_{50} = 200 µM). *Purity: ≥98% by HPLC.* M.W. 331.8



Cat. No. 528150 **1 mg** **€56**
5 mg **€164**

Ref.: Abdelkarim, G.E., et al. 2001. *Int. J. Mol. Med.* **7,** 255; Garcia-Soriano, F.G., et al. 2001. *Nature Med.* **7,** 108; Mabley, G.J., et al. 2001. *Inflamm. Res.* **50,** 561.

PARP Inhibitor X, TIQ-A

(4H-Thieno[2,3-c]isoquinolin-5-one)

A cell-permeable, potent inhibitor of PARP-1 (IC_{50} = 450 nM). *Purity: ≥98% by HPLC.* M.W. 201.2

Cat. No. 612100 **1 mg** **€77**

Ref.: Pellicciari, R., et al. 2003. *Farmaco* **58,** 851; Chiarugi, A., et al. 2003. *J. Pharmacol. Exp. Ther.* **305,** 943.

NEW PARP Inhibitor XI, DR2313

A water-soluble pyrimidinone compound that acts as a potent and NAD^+-competitive inhibitor of PARP (IC_{50} = 200 nM and 240 nM for rhPARP1 and rmPARP2, respectively). *Purity: ≥98% by HPLC.* M.W. 182.2

Cat. No. 528819 **5 mg** **€111**

Ref.: Nakajima, H., et al. 2005. *J. Pharmacol. Exp. Ther.* **312,** 472.

NEW Lipocortin-I, His•Tag®, *E. coli*

(Annexin-I, Human, Recombinant)

A full-length, recombinant, human, lipocortin-I expressed in *E. coli* with N-terminal His•Tag® and S•Tag™ sequences. Lipocortin can be phosphorylated at Tyr^{20} by EGFR, Abl, and Src; at Thr^{215} by PKA; and at Thr^{23} and Ser^{26} by PKC. Lipocortin-I is a Ca^{2+}/phospholipid-binding protein that promotes membrane fusion and exocytosis. *Purity: >90% by SDS-PAGE.*

Cat. No. 437621 **50 µg** **€70**

Ref.: White, I.J., et al. 2005. *EMBO J.* **25,** 1. Kusumawati, H., et al. 2001. *Cell Biol. Int.* **25,** 809. Lennon, G., et al. 1996. *Genomics* **33,** 151.

DNA-Dependent Protein Kinase (DNA-PK) Inhibitors

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

DNA-PK phosphorylates protein targets and also undergoes autophosphorylation. The autophosphorylation activity has been shown to be essential for repair of random double-strand breaks. DNA-PK phosphorylates p53 on Ser^{15} and Ser^{37} leading to stabilization and inhibition of p53 degradation by MDM2. Phosphorylation of Ser^{15} is suggested to be essential for p53 function. Ser^{15} resides within the critical N-terminal region of p53, which controls the interaction of p53 with the transcriptional apparatus and with the MDM2 protein. Phosphorylation of Ser^{15} weakens both the association of p53 with MDM2 and the repression of p53 by MDM2. Phosphorylation of DNA-PK by the PKCδ catalytic fragment leads to the dissociation of DNA-PK from DNA, resulting in its inactivation.

DNA-PK represents a new target for cancer drug development. Cells defective in DNA-PK components are reported to be hypersensitive to killing by ionizing radiation owing to their inability to repair double-stranded breaks effectively. A number of small molecule inhibitors of DNA-PK catalytic subunit have been developed, which sensitize cells to DNA-damaging agents, but are relatively nontoxic in the absence of DNA breaks. These inhibitors may have clinical potential in the treatment of cancer.

References:

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Wechsler, T., et al. 2004. *Proc. Natl. Acad. Sci. USA* **101,** 1247.
Basu, A., 2003. *J. Cell. Mol. Med.* **7,** 341.
Kashishian, A., et al. 2003. *Mol. Cancer Ther.* **2,** 1257.
Woo, R.A., et al. 1998. *Nature* **394,** 700.
Jackson, S.P. and Jeggo, P.A. 1995. *Trends Biochem. Sci.* **20,** 412.

DNA-PK Inhibitors

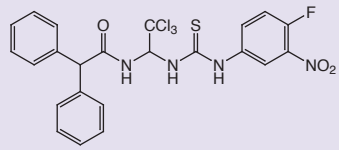
Name	Cat. No.	Comments	Size	Price
DNA-PK Inhibitor (4,5-Dimethoxy-2-nitrobenzaldehyde)	260960	A cell-permeable, potent, and selective inhibitor of DNA-PK (IC_{50} = 15 µM) and DNA-PK-mediated double strand break repair by non-homologous DNA-end-joining. Effectively sensitizes cells to killing by Cisplatin. *Purity:≥90% by GC.*	10 mg	€76
DNA-PK Inhibitor II (2-(Morpholin-4-yl)-benzo[h]chromen-4-one)	260961	A cell-permeable, potent, specific, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 230 nM). Inhibits DNA-PK-mediated, but not PARP-1-mediated double strand break repair and potentially lethal damage recovery following ionizing radiation treatment. Sensitizes both proliferating and quiescent cells to ionizing radiation. *Purity:≥98% by HPLC.*	5 mg	€150
DNA-PK Inhibitor III (1-(2-Hydroxy-4-morpholin-4-yl-phenyl)ethanone)	260962	A cell-permeable, potent, selective, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 120 nM) and PI 3-Kinase catalytic subunit p110β (IC_{50} = 135 nM). It inhibits DNA-PK-mediated double strand break repair (EC_{50} = 68 µM). Enhances DSB-induced anti-tumor activity both *in vitro* and *in vivo. Purity:≥95% by HPLC.*	1 mg	€98
DNA-PK Inhibitor IV (2-Hydroxy-4-morpholin-4-yl-benzaldehyde)	260963	A potent, selective, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 430 nM). *Purity:≥95% by HPLC.*	1 mg 5 mg	€87 €280
DNA-PK Inhibitor V (1-(2-Hydroxy-4-morpholin-4-yl-phenyl)-phenyl-methanone)	260964	A potent, selective, and ATP-competitive inhibitor of DNA-PK (IC_{50} = 270 nM). *Purity:≥95% by HPLC.*	1 mg 5 mg	€107 €352

Antibodies for DNA-Dependent Protein Kinase Research

Name	Cat. No.	Comments	Size	Price
Anti-DNA-PK (Ab-1) (2015-2134) Rabbit pAb	PC127	Liquid, purified. Immunogen used was a recombinant fusion protein containing amino acids 2015-2134 of the human DNA-PK catalytic subunit. Exhibits cross-reactivity in horse, human, mouse, rat, and *Xenopus*. **IB, IF, IP, PS**	100 µg	€277
Anti-DNA-PK (Ab-2) Mouse mAb (18-2)	NA57	Liquid, purified. Immunogen used was DNA-PK purified from HeLa cells. Recognizes the ~470 kDa human DNA-PK protein. **FS, IB, IF, IP, NT, PS**	100 µg	€294

FS: frozen sections; **IB**: immunoblotting; **IF**: immunofluorescence; **IP**: immunoprecipitation; **NT**: neutralization; **PS**: paraffin sections

ATM/ATR Kinase Inhibitor



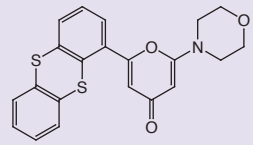
A cell-permeable thiourea compound that selectively inhibits the kinase activity of ATM and ATR (IC_{50} ~ 200 nM) without significantly affecting other PIKK family members (PI 3-K, mTOR, and DNA-PK) or kinases that are known to phosphorylate p53. *Purity: ≥95% by HPLC.* M.W. 555.8

Cat. No. 118501 **5 mg** **€163**

Ref.: Won, J., et al. 2006. *Nat. Chem. Biol.* **2,** 369.

ATM Kinase Inhibitor

(2-Morpholin-4-yl-6-thianthren-1-yl-pyran-4-one)



A cell-permeable, potent, and ATP-competitive inhibitor of ATM kinase (IC_{50} = 13 nM; K_i = 2.2 nM). Displays excellent selectivity over other PIKK family kinases (IC_{50} = 2.5, 9.3, 16.6 µM for DNA-PK, mTOR, PI 3-K, respectively; IC_{50} > 100 µM for PI 4-K and ATR). Inhibits ATM-dependent cellular protein phosphorylation following ionizing radiation treatment and sensitizes cells with wild-type ATM, but not mutant ATM, to the cytotoxic effects of DNA-damaging agents. *Purity: ≥98% by HPLC.* M.W. 395.5

Cat. No. 118500 **2 mg** **€83**

Ref.: Pereg, Y., et al. 2005. *Proc. Natl. Acad. Sci. USA* **102,** 5056; Lau, A., et al. 2005. *Nat. Cell Biol.* **7,** 493; Hickson, I., et al. 2004. *Cancer Res.* **64,** 9152.

Looking for p21-Activated Kinase Inhibitor?

p21-Activated Kinase Inhibitor, PAK18

A PAK (p21-activated kinase) inhibitor peptide containing the cell permeant TAT peptide sequence and an 18-mer Pro-rich PIX-interacting motif of PAK that disrupts PIX-PAK interaction and reduces cellular PAK phosphorylation. *Purity: ≥97% by HPLC.* M.W. 3413.9

Cat. No. 506101 **2 mg** **€200**

Ref.: Zhao, L., et al. 2006. *Nat. Neurosci.* **9,** 234; Maruta, H., et al. 2002. *Methods Mol. Biol.* **189,** 75.

Also available...

p21-Activated Kinase Inhibitor, Negative Control

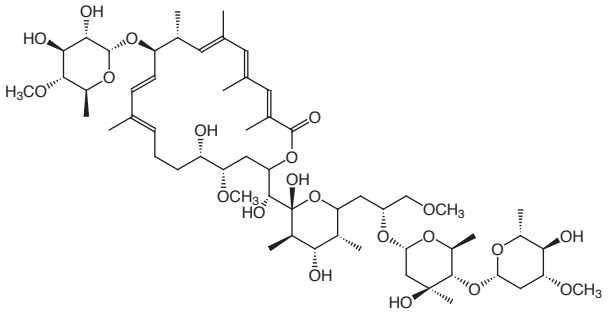
The inhibitory activity of p21-Activated Kinase Inhibitor PAK18 (Cat. No. 506101) is rendered inactive with a single amino acid mutation (R192A). *Purity: ≥97% by HPLC.* M.W. 3328.8

Cat. No. 506102 **2 mg** **€200**

NEW Apoptosis Activators

Apoptosis Activator IV, Apoptolidin

A cell-permeable macrolide antibiotic that induces apoptosis in E1A-transformed cells (IC_{50} = 11 ng/ml) with high selectivity. Its apoptotic activity correlates with its F_0F_1-ATPase inhibition (IC_{50} = 700 nM in yeast). Apoptolidin quickly isomerizes to and co-exists with Isoapoptolidin (Cat. No. 371959) in equilibrium (k_1 = 0.0656 h^{-1} and K_{eq} = 0.616 in Dulbecco's PBS at 37°C). *Purity: ≥95% by HPLC.* M.W. 1129.4



Cat. No. 178495 **100 µg** **€176**

Ref.: Daniel, P.T., et al. 2006. *Angew. Chem. Int. Ed. Engl.* **45,** 872; Wender, P.A., et al. 2002. *Org. Lett.* **4,** 3819; Salomon, A.R., et al. 2001. *Chem. Biol.* **8,** 71; Salomon, A.R., et al. *Proc. Natl. Acad. Sci. USA* **97,** 14766.

Apoptosis Activator V, Isoapoptolidin

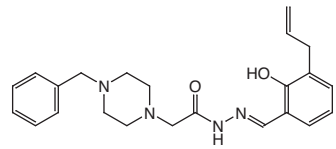
A cell-permeable ring-expanded macrolide isomer of Apoptolidin (Cat. No. 178495), but has lower inhibitory activity against F_0F_1-ATPase (IC_{50} = 17 µM in yeast). Isoapoptolidin quickly isomerizes to and co-exists with Apoptolidin in equilibrium (k_1 = 0.0626 h^{-1} and K_{eq} = 0.638 in Dulbecco's PBS at 37°C). *Purity: ≥90% by HPLC.* M.W. 1129.4

Cat. No. 371959 **100 µg** **€176**

Ref.: Wender, P.A., et al. 2002. *Chem. Lett.* **4,** 3819.

Procaspase-3 Activator, PAC-1

A cell-permeable activator of procaspase-3 (EC_{50} = 220 nM) that acts by overcoming the safety-catch-mediated suppression of caspase autoactivation. Substitution of any of the three aspartate residues in the enzyme's safety-catch region greatly reduce the *in vitro* activation efficiency (EC_{50} = 2.77 µM, 113 µM, and 131 µM for mutant procaspase-3 with DAD, DDA, and ADD sequence, respectively; EC_{50} = 4.5 µM for wild-type procaspase-7 with DTD sequence). *Purity: ≥95% by HPLC.* M.W. 392.5

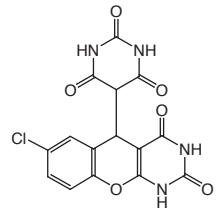


Cat. No. 529661 **10 mg** **€116**

Ref.: Putt, K.S., et al. 2006. *Nat. Chem. Biol.* **2,** 543.

Bcl-2 Inhibitor III, EM20-25

A cell-permeable pyrimidine-trione compound that binds to Bcl-2 and disrupts its interaction with Bax, and activates caspase-9. Sensitizes apoptosis-resistant, Bcl-2-overexpressing leukemic cells to cytotoxic drugs. Induces permeability transition pore opening in isolated mitochondria and in intact cells without affecting respiration. *Purity: ≥95% by elemental analysis.* M.W. 376.7

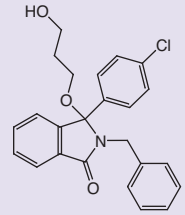


Cat. No. 197332 **10 mg** **€79**

Ref.: Milanesi, E., et al. 2006. *J. Biol. Chem.* **281,** 10066.

MDM2 Antagonist III

A cell-permeable isoindolinone compound that binds to MDM2 and disrupts MDM2-p53 interaction (IC_{50} = 15.9 µM) and upregulate cellular levels of MDM2 and p21 in SJSA cells. *Purity: ≥95% by HPLC.* M.W. 407.9



Cat. No. 444149 **10 mg** **€135**

Ref.: Hardcastle, I.R., et al. 2006. *J. Med. Chem.* **49,** 6209; Hardcastle, I.R., et al. 2006. *Bioorg. Med. Chem. Lett.* **15,** 1515.

NEW Viral Proteases

HCV NS3/4A Protease, Recombinant, *E. coli*

A recombinant, human Hepatitis C Virus (HCV) protease expressed in *E. coli* and purified by affinity chromatography using FPLC. HCV NS3/4A is an essential enzyme for viral replication and a potential target for anti-viral drugs for hepatitis C treatment. *Biological activity: 20-200 ng is sufficient for an in vitro protease assay. One unit is defined as 1 ng of purified protein. Purity: ≥95% by SDS-PAGE.*

Cat. No. 444147 **10,000 units** **€320**

HIV-1 Protease, Recombinant, *E. coli*

A recombinant HIV-1 protease expressed in *E. coli* and purified by affinity chromatography using FPLC. HIV-1 (Human Immunodeficiency Virus type 1) protease is an aspartic protease that functions only as a dimer and is essential for the maturation of new infectious virions. A crucial target for developing inhibitors of HIV-1 replication. *Biological activity: 20-200 ng is sufficient for an in vitro protease assay. Purity: ≥85% by SDS-PAGE.*

Cat. No. 382136 **10,000 units** **€320**

West Nile Virus NS3 Protease, Recombinant, *E. coli*

A recombinant, human West Nile virus proteinase (WNV NS2B-NS3pro) expressed in *E. coli* as a fusion protein with the cofactor, NS2B, and a C-terminal His•Tag® sequence. Amino acids 1476-1687 of the West Nile polyprotein precursor are fused to amino acids 1393-1440 of NS2B via a 9-amino acid linker (GGGGSGGGG). The C-terminal lysine (Lys48) is mutated to alanine to inactivate autolytic cleavage and improve stability. West Nile Virus NS3 protease is a potential target for the development of antiviral agents that block viral replication. *Specific activity: ≥1 µmol/min/mg protein. Purity: ≥95% by SDS-PAGE.*

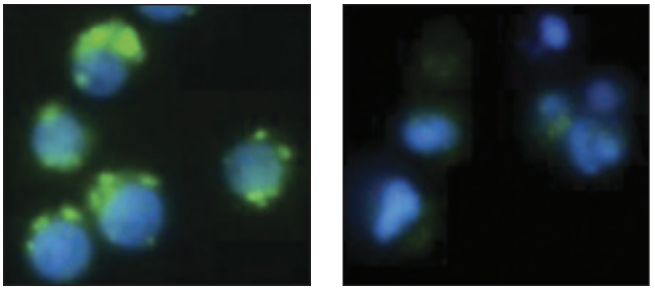
Cat. No. 444148 **25 µg** **€274**

Add Convenience to your life and save time with our NEW kits for Apoptosis Research

NEW InnoCyte™ Flow Cytometric Cytochrome *c* Release Kit

A convenient and sensitive assay for determination of the re-localization of cytochrome *c* from the mitochondria to the cytoplasm using flow cytometry or fluorescence microscopy. The kit provides a rapid method for inhibitor screening and assessing the regulation of apoptotic signaling in cells. It relies on the selective permeabilization of the cellular membrane for release of cytosolic components while leaving the mitochondrial membrane intact. Viable cells display mitochondrial staining of cytochrome *c*. Apoptotic cells do not stain since they release cytochrome *c* into the cytosol.

Cat. No. CBA077 **1 kit** **€231**



- Act D + Act D

Jurkat cells (4×10^5) either untreated (left panel) or treated (right panel) with 1 mM Actinomycin D (Cat. No. 114666) for 8 h. Cytochrome *c* is retained in the mitochondria in viable cells (arrows, left panel) and is lost from cells treated with Actinomycin D (right panel).

NEW Apoptosis Research kits *(continued...)*

NEW Annexin V-Biotin Apoptosis Detection Kit II

A convenient kit for the identification of changes in the plasma membrane during apoptosis. In apoptotic cells, phosphoatidylserine (PS) is translocated from the inner to the outer leaflet of the plasma membrane, allowing for the detection of PS on the cell surface. In the presence of Ca^{2+}, Annexin V exhibits a high affinity for PS and binds cells with exposed PS. Annexin V, when conjugated to biotin or to a fluorophore, can be used to monitor apoptopic cells using flow cytometry or immunofluorescence microscopy.

Cat. No. CBA058 **1 kit** **€153**

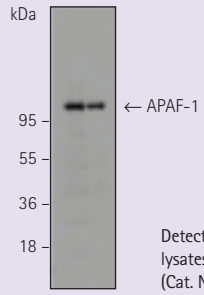
Pifithrins: Inhibitors of p53 Action

Name	Cat. No.	Comments	Size	Price
Pifithrin-α	506132	A cell-permeable chemical inhibitor of p53. Reversibly inhibits p53-dependent transactivation of p53-responsive genes and reversibly blocks p53-mediated apoptosis. Protects neurons against β-amyloid peptide and glutamate-induced apoptosis.	5 mg 10 mg	€81 €140
Pifithrin-α, Cyclic-	506134	A cell-permeable, very stable analog of Pifithrin-α, with similar biological function, but with reduced cytotoxicity.	10 mg	€153
Pifithrin-α, *p*-Nitro	506152	A cell-permeable p53 inhibitor that serves as the pro-drug form of Pifithrin-α, *p*-Nitro, Cyclic (Cat. No. 506154). It is 100-fold more potent than Pifithrin-α when administered in rats due to its long-lasting, steady conversion to the corresponding cyclic form of active compound ($t_{1/2}$ = 8 h in neuron cultures).	5 mg	€79
Pifithrin-α, *p*-Nitro, Cyclic	506154	A cell-permeable p53 inhibitor with 10-fold higher potency and 50% longer half-life ($t_{1/2}$ = 6 h in neuron cultures) than Pifithrin-α (Cat. No. 506132). Despite its *in vitro* efficacy, this inhibitor is not effective *in vivo*. For *in vivo* applications, please consider Pifithrin-α, *p*-Nitro (Cat. No. 506152).	5 mg	€89
Pifithrin-μ	506155	A cell-permeable sulfonamide that blocks p53 interaction with Bcl-xL and Bcl-2. Selectively inhibits p53 translocation to mitochondria without affecting the transactivation function of p53. Targets only the mitochondrial branch of the p53 pathway and is superior to Pifithrin-α (Cat. No. 506132) in *in vivo* studies.	10 mg	€83

Anti-APAF-1 Mouse mAb (94408)

Lyophilized, protein G purified. Immunogen used was recombinant protein containing amino acids 10-214 of human APAF-1. Recognizes the ~130 kDa apoptosis protease activating factor 1 protein (APAF-1) in Jurkat cells. Suitable for immunoblotting.

Cat. No. AP1038 **100 µg** **€274**



Detection of APAF-1 by immunoblotting. Sample: Jurkat cell lysates. Primary antibody: Anti-APAF-1 Mouse mAb (94408) (Cat. No. AP1038) (1 µg/ml). Detection: chemiluminescence.

NEW Protein Kinase Inhibitors

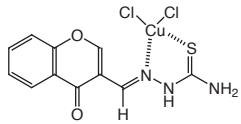
Name	Cat. No.	Comments	Size	Price
Aurora Kinase/Cdk Inhibitor	189406	A cell-permeable, reversible, ATP-competitive inhibitor with selectivity towards Aurora kinases (IC_{50} = 11 and 15 nM for Aurora-A, Aurora-B, respectively) and Cdk's (IC_{50} = 9, 4, and 3 nM for Cdk1/B, Cdk2/A, and Cdk2/E, respectively).	5 mg	€209
EGFR/ErbB-2/ErbB-4 Inhibitor	324840	A cell-permeable, potent, ATP-competitive, irreversible inhibitor of erbB kinase activity (IC_{50} = 0.3, 1.1, and 0.5 nM for erbB-1, erbB-2, and erbB-4, respectively).	1 mg	€121
EGFR Inhibitor II, BIBX1382	324832	A cell-permeable, potent, reversible, ATP-competitive, and highly selective inhibitor of the kinase activity of EGFR (ErbB-1) in cell-free reactions (IC_{50} = 3 nM) and in cultures (IC_{50} = 0.15, 1.82, and 3.2 µM in EGF-, HGF-, and FCS-dependent thymidine incorporation, respectively, in KB cells). Exhibits 1,000-fold greater selectivity over ErbB-2 (IC_{50} = 3.4 µM).	5 mg	€163
JNK Inhibitor VIII	420135	A cell-permeable, ATP-competitive, reversible inhibitor of JNK (K_i = 2 nM, 4 nM, and 52 nM for JNK1, 2 and 3, respectively)	5 mg	€148
PDGF Receptor Tyrosine Kinase Inhibitor V	521234	A cell-permeable, potent, ATP-competitive, and reversible inhibitor of the tyrosine kinase activity of PDGFR (IC_{50} = 4 and 7.6 nM). Inhibits c-kit receptor kinase activity only at much higher concentration (IC_{50} = 234 nM).	1 mg	€153
Raf Kinase Inhibitor III	553013	A cell-permeable, potent, reversible, and highly selective inhibitor of Raf kinase (K_d = 300 pM for B-Raf).	1 mg	€135
Syk Inhibitor III (3,4-Methylenedioxy-β-nitrostyrene)	574713	A cell-permeable, selective inhibitor of Syk activity (IC_{50} = 2.5 µM). It inhibits Src only at much higher concentrations (IC_{50} = 29.3 µM).	50 mg	€79
Syk Inhibitor IV, BAY 61-3606	574714	A cell-permeable, potent, ATP-competitive, reversible, and highly selective inhibitor of Syk tyrosine kinase activity (IC_{50} = 10 nM).	2 mg	€122

NEW Inhibitors of Akt/PI-3 Kinase Signaling

Akt Inhibitor XI

(3-Formylchromone thiosemicarbazone, Cu(II)Cl2 Complex)

A cell-permeable copper complex (Cu^{2+}/Cu^{+} redox couple) that interacts with both the PH and the kinase domains of Akt and inhibits its activity (IC_{50} = 100 nM). *Purity: ≥98% by Elemental Analysis.* M.W. 381.7



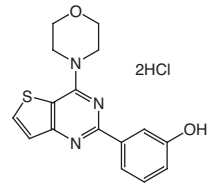
Cat. No. 124028 **5 mg** **€167**

Ref.: Barve, V., et al. 2006. *J. Med. Chem* **49,** 3800

PI 3-Kα Inhibitor IV

(3-(4-Morpholinothieno[3,2-d]pyrimidin-2-yl)phenol, HCl)

A cell-permeable, potent, and isoform-selective inhibitor of PI 3-K (IC_{50} = 2 nM, 16 nM, 660 nM, and 220 nM for p110α, p110β, p110γ, and PI 3-K C2β, respectively). *Purity: ≥95% by HPLC.* M.W. 386.3

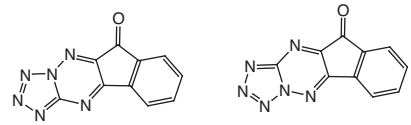


Cat. No. 528111 **5 mg** **€167**

Ref.: Hayakawa, M., et al. 2006. *Bioorg. Med. Chem.* **14,** 6847.

PDK1/Akt/Flt Dual Pathway Inhibitor

([1,2-6H-Indeno e]tetrazolo[1,5-b][1,2,4]triazin-6-one & 10H-Indeno [2,1-e]tetrazolo[1,5-b][1,2,4]triazin-10-one)



A cell-permeable inhibitor of both PDK1 and Akt activities in *in vitro* kinase assays. Its dual inhibitory nature against both PDK1/Akt and Flt3/PIM signaling allows effective killing of AML cells (Average IC_{50} = 1.05, 1.91, and 0.43 µM for AML with wild-type Flt3, single mutant ITD/D835, and double mutant Flt3-ITD-TDK, respectively) that are otherwise resistant to inhibitors that target only the PDK1/Akt pathway. Blocks cellular phosphorylation of Akt at both Ser^{473} and Thr^{308}. *Purity: ≥98% by HPLC (sum of two isomers).* M.W. 224.2

Cat. No. 521275 **5 mg** **€209**

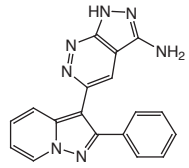
Ref.: Zeng, Z., et al. 2006. *Cancer Res.* **66,** 3737; Koul, D., et al. 2006. *Mol. Cancer Ther.* **5,** 637; Mandal. M., et al. 2006. *Oral Oncol.* **42,** 430; Mandal. M., et al. 2005. *Br. J. Cancer* **92,** 1899.

NEW ERK Inhibitors

ERK Inhibitor II

(5-(2-Phenyl-pyrazolo[1,5-a]pyridin-3-yl)-1H-pyrazolo[3,4-c]pyridazin-3-ylamine)

A cell-permeable, potent, ATP-competitive inhibitor of ERK1 and ERK2 (IC_{50} = 510 nM and 330 nM; K_i = 310 nM and 140 nM, respectively). Exhibits ~20-fold greater selectivity over p38α (IC_{50} = 10 µM) and trivial activity towards IKKα, MEK1, MKK4, PDGFRα, PKCα, Src, and Syk even at 30 µM. *Purity: ≥98% by HPLC.* M.W. 327.3

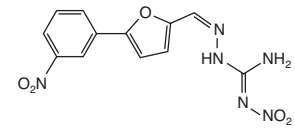


Cat. No. 328007 **1 mg** **€126**

Ref.: Ohori, M., et al. 2005. *Biochem. Biophys. Res. Commun.* **336,** 357.

ERK Inhibitor III

A cell-permeable furanyl-nitroaminoguanidine ERK-binding (K_d of ~13 µM) compound that acts as a substrate-, but not ATP-, site-targeting inhibitor of ERK. Selectively inhibits the EGF-stimulated cellular phosphorylation of ERK substrates Rsk-1 and Elk-1, but not that of ERK1/2 or the anisomycin-induced phosphorylation of the p38 substrate ATP-2 in HeLa cells. *Purity: ≥85% by HPLC.* M.W. 318.3



Cat. No. 328009 **5 mg** **€86**

Ref.: Chen, F., et al. 2006. *Bioorg. Med. Chem. Lett.* **16,** 6281.

ERK Inhibitor II, Negative Control

(5-(2-Phenyl-pyrazolo[1,5-a]pyridin-3-yl)-1H-pyrazolo[3,4-c]pyridazin-3-ol)

A cell-permeable pyrazolopyridazinol that serves as a negative control for ERK Inhibitor II (Cat. No. 328007). Shown to exhibit little activity towards ERK1 and ERK2 (IC_{50} > 100 µM). *Purity: ≥98% by HPLC.* M.W. 328.3

Cat. No. 328008 **1 mg** **€126**

Ref.: Ohori, M., et al. 2005. *Biochem. Biophys. Res. Commun.* **336,** 357.

Want to preserve your stained tissue sections?

FluorSave™ Reagent

Aqueous mounting medium for use in conjunction with fluorescent tracers such as fluorescein, rhodamine, and phycobiliprotein probes. Preserves fluorescence-stained tissue sections. Specially formulated without glycerol. Ideal for preservation of phycoerythrin, phycocyanin, or allophycocyanin stained tissue samples.

Cat. No. 345789 **20 ml** **€67**

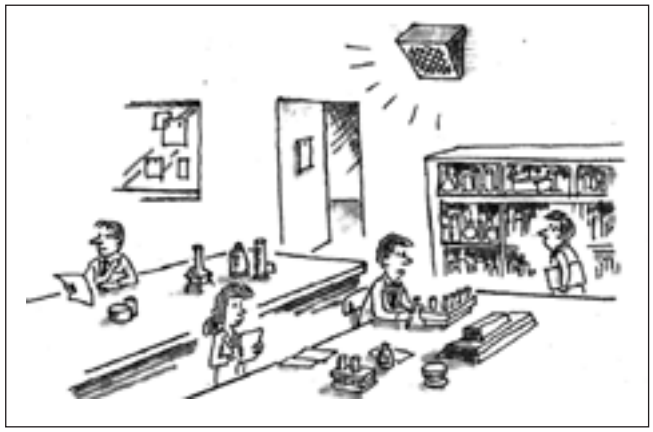
ChromoSave™ Reagent

A water-based mounting medium for permanent preservation of alkaline phosphatase and immuno-peroxidase stained cells and tissue sections. Compatible with fluorescein, rhodamine, and TEXAS RED® stained tissues.

Cat. No. 238540 **30 ml** **€82**

NEW Recombinant Protein Tyrosine Kinases

Name	Cat. No.	Comments	Size	Price
EPHB4, GST-Fusion, Human, Recombinant, *S. frugiperda*	324783	EPHB4 is a receptor for Ephrin-B2 and is involved in short-range, contact-mediated, axonal guidance and angiogenesis. Aberrant expression of EPHB4 has been reported in prostate cancer and highly malignant breast cancers. *Specific activity: ≥60 pmol/min/µg protein.*	10 µg	€265
ErbB4, GST-Fusion, Human, Recombinant, *S. frugiperda*	324785	A member of the signaling network composed of the EGF family of growth factors and the ErbB family of receptor tyrosine kinases. Plays an important role in cardiovascular and neural development and differentiation of the mammary gland. *Specific activity: ≥20 pmol/ µg protein.*	10 µg	€257
FAK, GST-Fusion, Human, Recombinant, *S. frugiperda*	324876	A non-receptor tyrosine kinase that plays a central role in cell spreading, differentiation, migration, cell death, and acceleration of the G1 to S phase transition of the cell cycle. *Specific activity: ≥1 pmol/min/µg protein.*	10 µg	€265
FGF-R1, GST-Fusion, Human, Recombinant, *S. frugiperda*	325877	FGFR1 is a receptor tyrosine kinase that is involved in cell division, regulation of cell growth and maturation, formation of blood vessels, wound healing, and embryo development. *Specific activity: ≥15 pmol/min/µg protein.*	10 µg	€265
FGF-R3, GST-Fusion, Human, Recombinant, *S. frugiperda*	325878	FGF-R3 is a receptor tyrosine kinase is involved in the development and maintenance of bone and brain tissue. *Specific activity: ≥7 pmol/min/µg protein.*	10 µg	€265
FGR, GST-Fusion, Human, Recombinant, *S. frugiperda*	325879	A member of the Src tyrosine kinase family that is highly expressed in myelomonocytic cells. It has been reported to play a role in β2-integrin signaling. *Specific activity: ≥10 pmol/min/µg protein.*	10 µg	€265
IGF-1R, GST-Fusion, Human, Recombinant, *S. frugiperda*	325881	A tyrosine kinase receptor that mediates cell survival and growth in response to its ligands, IGF-1 and IGF-2. It is also involved in the proliferation of transformed cells. *Specific activity:≥45 pmol/min/µg protein.*	10 µg	€265
JAK3, GST-Fusion, Human, Recombinant, *S. frugiperda*	325883	JAK3 is a member of the Janus family of tyrosine kinases and plays an important role in signal transduction and interacts with members of the STAT (signal transduction and activators of transcription) family. *Specific activity: ≥6 pmol/min/µg*	10 µg	€265
MET, GST-Fusion, Human, Recombinant, *S. frugiperda*	325885	c-Met is a receptor tyrosine kinase activated by hepatocyte growth factor (HGF)/scatter factor (SF). It has been identified as a cell surface receptor for hepatocyte growth factor, a plasminogen-like protein thought to be a humoral mediator of liver regeneration. *Specific activity: ≥30 pmol/min/µg protein.*	10 µg	€265
MuSK, GST-Fusion, Human, Recombinant, *S. frugiperda*	325887	MuSK is a receptor tyrosine kinase that is expressed in early myotomes and developing muscle. It localizes to the neuromuscular junction and is a key mediator of agrin's action. *Specific activity:≥15 pmol/min/µg protein*	10 µg	€265
PDGFR-α, GST-Fusion, Human, Recombinant, *S. frugiperda*	325891	PDGFR-α is a member of the protein tyrosine kinase family that binds to PDGFA and PDGFB. It is believed that PDGFR-α is associated with a genetic susceptibility to human neural tube defects. *Specific activity: ≥8 pmol/min/µg protein.*	10 µg	€257
PDGFR-β, GST-Fusion, Human, Recombinant, *S. frugiperda*	325892	PDGFR-β is a member of the protein tyrosine kinase family of receptors that binds to PDGFA. It phosphorylates Tyr residues at the C-terminus of PTPN11, creating a binding site for the SH2 domain of GRB2. *Specific activity: ≥6 pmol/min/µg protein.*	10 µg	€257
SYK, GST-Fusion, Human, Recombinant, *S. frugiperda*	325893	A member of the SYK/ZAP-70 protein tyrosine kinase subfamily that acts as a positive effector of B-cell receptor-stimulated responses. Couples with the B cell receptor to affect the mobilization of calcium either through a PI 3K-dependent pathway or through a phospholipase Cγ-dependent pathway, when phosphorylated on Tyr^{342} and Tyr^{346}. *Specific activity: ≥10 pmol/min/µg protein.*	10 µg	€257



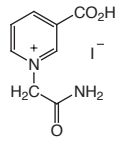
"Attention everybody: the lunch mobile just called. They are down to their very last spicy chicken burrito. You may place your bids at the reception desk."

Neurochemical Corner

NAADP Receptor Modulator

(1-Carbamoylmethyl-3-carboxy-pyridinium iodide)

A cell-permeable nicotinic acid analog that acts as a selective antagonist of NAADP-induced Ca^{2+} release. A weak NAADP receptor ligand (IC_{50} = 90 µM in competition binding against 0.2 nM NAADP) that specifically inhibits NAADP-mediated, but not cADPR-, IP_3-, or Acetylcholine-evoked, Ca^{2+} response. *Purity: ≥98% by HPLC.* M.W. 308.1



Cat. No. 481919 **25 mg** **€121**

Ref.: Dowden, J., et al. 2006. *Chem. Biol.* **13,** 659.

$S1P_2$ Receptor Antagonist, JTE-013

(1-(1,3-Dimethyl-4-isopropyl)-1H-pyrazolo[3,4-b]pyridin-6-yl)-4-(3,5-dichloro-4-pyridinyl)-semicarbazide JTE-013)

A cell-permeable, potent $S1P_2$-selective antagonist (IC_{50} = 17 nM and 22 nM in CHO cells stably transfected with human $S1P_2$ and rat $S1P_2$, respectively; IC_{50} > 10 µM for $S1P_1$ and $S1P_3$). Specifically blocks S1P binding to $S1P_2$ and prevents $S1P_2$-mediated intracellular Ca^{2+}-mobilization and ERK activation. Reverses the regulatory actions of S1P (Cat. No. 567727) on cell migration and invasion, cAMP accumulation and RANTES production. *Purity: ≥98% by HPLC.* M.W. 408.3

Cat. No. 567736 **5 mg** **€134**

Ref.: Damirin, A., et al. 2005. *Mol. Pharmacol.* **67,** 1177; Kawata, T., et al. 2005. *Biochem. Biophys. Res. Commun.* **331,** 640; Ikeda, H., et al. 2004. *Biochem. Biophys. Res. Commun.* **320,** 754; Arikawa, K., et al. 2003. *J. Biol. Chem.* **278,** 32841; Osada, M., et al. 2002. *Biochem. Biophys. Res. Commun.* **299,** 483.

Nemadipine-A

(Diethyl-4-(2,3,4,5,6-pentafluoro)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate)

A cell-permeable 1,4-dihydropyridine (DHP) compound that is shown to antagonize the α1-subunit of L-type calcium channel and its associated functions in *C. elegans* and in chick ciliary neurons. *Purity: ≥97% by HPLC.* M.W. 419.4

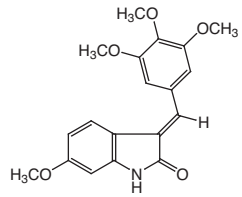
Cat. No. 480022 **25 mg** **€126**

Ref.: Kwok, T. C. Y., et al. 2006. *Nature* **441,** 91

Tubulin Polymerization Inhibitor II

((E)-1,3-Dihydro-6-methoxy-3-(3,4,5-trimethoxybenzylidene)-1H-indol-2-one

A cell-permeable, SU5416 (Cat. Nos. 676487 and 676498) derived combretastatin A-4 analog that acts as an effective anti-microtubule agent (IC_{50} = 4.5 µM in inhibiting polymerization of purified porcine brain tubulin). Also displays extremely potent anti-proliferative activity towards various cancer cell lines (GI_{50} <10 nM for 46 lines among a 53 NCI panel tested). *Purity: ≥97% by HPLC.* M.W. 341.4



Cat. No. 654164 **5 mg** **€81**

Ref.: Pandit, B., et al. 2006. *Bioorg. Med. Chem.* **14,** 6492; Li, P.K., et al. 2005. *Bioorg. Med. Chem. Lett.* **15,** 5382.

Tubulin-α-1, His•Tag® fusion, *E. coli*

Full-length, recombinant, human tubulin-α-1 (TBA1, TUBA1, α-tubulin 1) expressed in *E. coli* with N-terminal His•Tag® and S•Tag™ sequences. This preparation is qualified for use as a substrate for protein tyrosine kinases in *in vitro* assays. *Purity: ≥90% by SDS-PAGE.*

Cat. No. 654161 **50 µg** **€116**

Ref.: Lennon, G., et al. 1996. *Genomics* **33,** 151; Cox, M.E. and Maness, P.F. 1993. *J. Mol. Neurosci.* **4,** 63; Matten, W.T., et al. 1990. *J. Cell. Biol.* **111,** 1959.

Tubulin-γ-1, His•Tag® fusion, *E. coli*

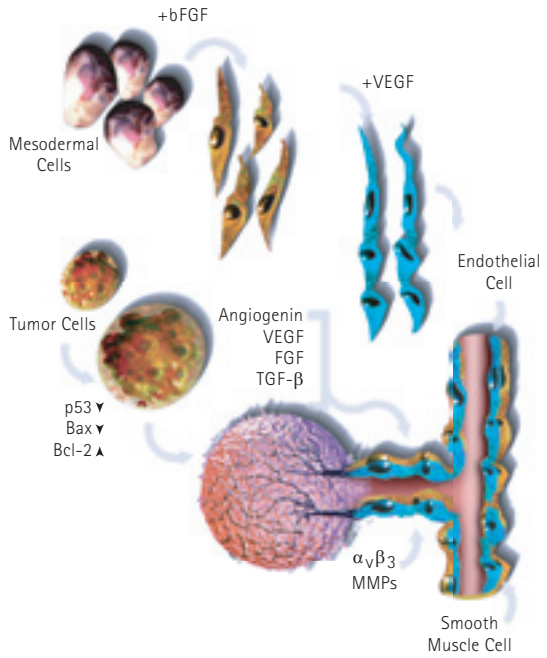
Full-length, recombinant, human tubulin-γ-1 (GCP-1, γ-1 tubulin) expressed in *E. coli* with N-terminal His•Tag® and S•Tag™ sequences. This preparation is qualified for use as a substrate for protein tyrosine kinases in *in vitro* assays. *Purity: ≥90% by SDS-PAGE.*

Cat. No. 654163 **50 µg** **€116**

Ref.: Kukharskyy, V., et al. 2004. *Exp. Cell Res.* **298,** 218; Lennon, G., et al. 1996. *Genomics* **33,** 151.

Angiogenesis: Role of VEGF in Endothelial Cell Proliferation

Angiogenesis is not only a prerequisite for tumor growth and expression, but also a major factor affecting the metastatic spread of malignant cells. Vascular endothelial growth factor (VEGF), one of the most potent angiogenic cytokines, regulates both vascular proliferation and permeability, and acts as an anti-apoptotic factor for newly formed blood vessels. Alternative splicing of a single VEGF gene results in the generation of five isoforms of VEGF, which differ in their molecular weights and in their ability to bind to cell-surface heparan sulfate proteoglycans. $VEGF_{121}$ and $VEGF_{165}$ are reported to be the most dominantly expressed variants in all tumor cell lines investigated. The biological effects of VEGF are mediated through two VEGF receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), whose expression is largely limited to the vascular endothelium. VEGF has been implicated as the major prognostic factor in tumor growth and angiogenesis. Its expression is enhanced in response to hypoxia, oncogenes, and several cytokines. VEGF is also associated with poor prognosis in several types of cancer.

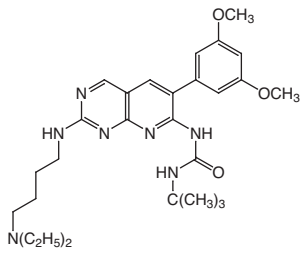


NEW Inhibitors for Angiogenesis Research

FGF/VEGF Receptor Tyrosine Kinase Inhibitor, PD173074

(1-t-Butyl-3-(6-(3,5-dimethoxyphenyl)-2-(4-diethylaminobutylamino)-pyrido [2,3-d]pyrimidin-7-yl)urea)

A cell-permeable, potent, ATP-competitive, and reversible inhibitor of tyrosine kinase activities of FGF and VEGF receptors (IC_{50} = 21.5 nM for FGFR1). Shown to inhibit the autophosphorylation of endogenous FGFR1 (IC_{50} <5 nM) and over-expressed VEGFR2 (IC_{50} <200 nM) in NIH3T3 cells *in vitro*, and FGF- and VEGF-induced angiogenesis in mice *in vivo*. *Purity:* ≥*97% by HPLC.* M.W. 523.7



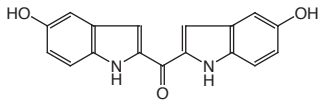
Cat. No. 341607 **2 mg** **€116**

Ref.: Koziczak, M., et al. 2004. *Oncogene* **23,** 350; Skaper, S.D., et al. 2000. *J. Neurochem.* **75,** 1520; Mohammadi, M., et al. 1998. *EMBO J.* **17,** 5896.

Flt3 Inhibitor II

(Bis-(5-hydroxy-1H-indol-2-yl)methanone)

A cell-permeable, ATP-competitive inhibitor of Flt3 (IC_{50} = 33 nM for hFlt3 and 40 nM in EOL-1 cells). Exhibits moderate selectivity over PDGFR (IC_{50} = 171 nM for hPDGFRβ and 300 nM in Swiss 3T3 fibroblasts).



Cat. No. 343021 **1 mg** **€130**

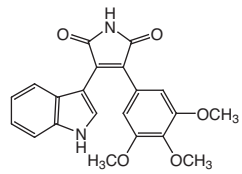
Ref.: Mahboobi, S., et al. 2006. *J. Med. Chem.* **49,** 3101.

NEW Inhibitors for Angiogenesis Research *(continued...)*

VEGF Receptor 2/3 Tyrosine Kinase Inhibitor

(3-(Indole-3-yl)-4-(3,4,5-trimethoxyphenyl)-1H-pyrrole-2,5-dione)

A cell-permeable 2,3-diarylmaleimide compound that acts as a potent and ATP-competitive inhibitor of VEGFR-2 and -3 (IC_{50} = 2.5 nM and 5 nM, respectively) with >100-fold selectivity over 25 other commonly studied kinases. Exhibits excellent *in vivo* anti-angiogenic efficacy in chick embryo assay (81.7% inhibition of vessel area at the vasculosa site with agarose pellets containing 150 µg inhibitor). *Purity: ≥97% by HPLC.* M.W. 387.4



Cat. No. 676499 **5 mg** **€144**

Ref.: Peifer, C., et al. 2006. *J. Med. Chem.* **49,** 7549.

Receptor Tyrosine Kinases for Angiogenesis Research

Flt-3, GST-Fusion, Human, Recombinant, *S. frugiperda*

Recombinant, human FMS-like Tyrosine Kinase 3 (Flt-3) fused at the N-terminus to a GST-His_6-thrombin cleavage site sequence and expressed in *S. frugiperda* using a baculovirus expression system. A class III receptor tyrosine kinase that is closely related to c-Kit and c-Fms. It is expressed in primitive hematopoietic cells, placenta, testis, spleen, thymus, bone marrow, brain and in cerebellar Purkinje cells. *Specific activity: ≥25 pmol/min/µg protein.*

Cat. No. 325880 **10 µg** **€265**

Ref.: Wodnar-Filipowicz, A., 2003. *News Physiol. Sci.* **18,** 247; Beslu, N., et al. 1996. *J. Biol. Chem.* **271,** 20075; Maroc, N., et al. 1993. *Oncogene* **8,** 909.

Tie2, GST-Fusion, Human, Recombinant, *S. frugiperda*

Recombinant, human Tie2 fused to a GST-His_6-thrombin cleavage site sequence at the N-terminus and expressed in *S. frugiperda* insect cells using a baculovirus expression system. Tie2 is a receptor tyrosine kinase that acts as the transmembrane receptor for angiopoietin and plays an important role in endothelial cell proliferation and differentiation. *Specific activity: ≥95 units/µg protein.* M.W. 66,882.

Cat. No. 325894 **10 µg** **€257**

Ref.: Park, E.H., et al. 2005. *J. Biol. Chem.* **280,** 20945; Hashimoto, T., et al. 2004. *Endothelium* **11,** 207; Vikkula, M., et al. 1996. *Cell* **87,** 1181.

Tie2, His•Tag®, Human, Recombinant, *S. frugiperda*

Recombinant, human Tie2 fused to a His•Tag® sequence at the N-terminus and expressed in *Spodoptera frugiperda* insect cells using a baculovirus expression system. Tie2 is a type 1 membrane receptor protein specifically expressed in developing vascular endothelial cells and their progenitors, angioblasts. It is also found in placenta and lung, with lower levels in umbilical vein endothelial cells, brain, and kidney. *Specific activity: ≥140 units/µg protein.*

Cat. No. 124024 **10 µg** **€265**

Ref.: De Palma, M., et al. 2005. *Cancer Cell* **8,** 211; Partanen, J., and Dumont, D.J., 1999. *Curr. Top. Microbiol. Immunol.* **237,** 159.

VEGF-R1, GST-Fusion, Human, Recombinant, *S. frugiperda*

Recombinant, human vascular endothelial growth factor receptor 1 (VEGF-R1) fused to a GST-His_6-thrombin cleavage site sequence at the N-terminus and expressed in *S. frugiperda* insect cells using a baculovirus expression system. VEGF-R1 is a receptor tyrosine kinase that plays an important role in vascular development and regulation of vascular permeability. *Specific activity: ≥45 pmol/min/µg protein.* M.W. 89,357.

Cat. No. 325895 **10 µg** **€257**

Ref.: Lenz, T., et al. 2005. *Nephrology* **10,** 84; Sartelet, H., et al. 2004. *Hum. Pathol.* **35,** 1210; Orecchia, A., et al. 2003. *J. Cell Sci.* **116,** 3479; Shibuya, M., et al. 1990. *Oncogene* **5,** 519.

PhosphoDetect™ Antibodies for Vascular Endothelial Growth Factor (VEGF) Receptor

Name	Cat. No.	Comments	Size	Price
PhosphoDetect™ Anti-VEGFR2 (pTyr$^{1054/1059}$) Rabbit pAb	PS1013	Liquid, immunoaffinity purified. Immunogen used was a synthetic phosphopeptide corresponding to amino acids surrounding the Tyr$^{1054/1059}$ phosphorylation sites of mouse and human VEGFR-2. Recognizes the ~200 kDa VEGFR-2 protein phosphorylated at Tyr$^{1054/1059}$ in porcine pancreatic cells transfected with a CSF-1/mouse VEGFR-2 chimeric receptor. **IB**	10 T	€304
PhosphoDetect™ Anti-VEGFR2 (pTyr^{1214}) Rabbit pAb	PS1012	Liquid, immunoaffinity purified. Immunogen used was a synthetic phosphopeptide corresponding to amino acids surrounding the Tyr^{1214} phosphorylation site of human VEGFR-2. Recognizes the ~200 kDa VEGFR-2 phosphorylated at Tyr^{1214}. **IB**	10 T	€304
PhosphoDetect™ Anti-VEGF Receptor 1 (Ab-2) (pTyr^{1213}) Rabbit pAb	PC459	Undiluted serum. Immunogen used was a synthetic phosphopeptide corresponding to amino acids 1208-1218 of human VEGF-R1. Recognizes VEGF-R1 phosphorylated at Tyr^{1213}. **ELISA, PS**	25 µl	€245
PhosphoDetect™ Anti-VEGF Receptor 2/3 (pAb-1) Rabbit pAb	PC460	Undiluted serum. Immunogen used was a synthetic phosphopeptide [GLARDIpYKDPDpYVRKGD(C)] corresponding to amino acids in human VEGF Receptor 2/3. Recognizes phosphorylated VEGF Receptor 2/3. **IB, PS**	25 µl	€245

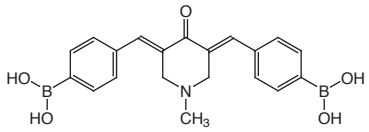
ELISA: enzyme-linked immunosorbent assay; **IB**: immunoblotting; **PS**: paraffin sections

Interested in Proteasome/Ubiquitination Research?

Proteasome Inhibitor IX, AM114

(3,5-bis-(4-Boronic acid-benzylidene)-1-methylpiperidin-4-one)

A cell-permeable boronate chalcone compound with ~ 30-fold higher potency than MG-132 (Cat. No. 474790) in inhibiting chymotrypsin-like activity of 20S proteasome (IC_{50} ~ 1 µM). *Purity: ≥95% by HPLC.* M.W. 377.0



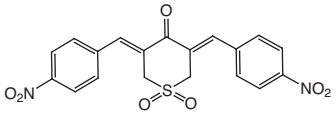
Cat. No. 539184 **10 mg** **€111**

Ref.: Achanta, G., et al. 2006. *Mol. Pharmacol.* **70,** 426; Modzelewska, A., et al. 2006. *Bioorg. Med. Chem.* **14,** 3491.

NEW Ubiquitin Isopeptidase Inhibitor I, G5

(NSC-144303)

A cell-permeable cross-conjugated α,β-unsaturated dienone compound that induces caspase activation and apoptosis (IC_{50} = 1.76 and 1.6 µM in E1A and E1A/C9DN cells, respectively) via the apoptosome-independent mitochondrial pathway by selectively inhibiting ubiquitin isopeptidase activity (IC_{50} ~ 30 µM). *Purity: ≥97% by HPLC.* M.W. 414.4



Cat. No. 662125 **10 mg** **€108**

Ref.: Aleo, E., et al. 2006. *Cancer Res.* **66,** 9235.

NEW Ubiquitin Isopeptidase Inhibitor II, F6

(NSC-632839)

A cell-permeable cross-conjugated α,β-unsaturated dienone compound that induces caspase activation and apoptosis (IC_{50} = 15.65 and 16.23 µM in E1A and E1A/C9DN cells, respectively) via the apoptosome-independent mitochondrial pathway by selectively inhibiting ubiquitin isopeptidase activity. *Purity: ≥97% by HPLC.* M.W. 303.4

Cat. No. 662126 **10 mg** **€98**

Ref.: Aleo, E., et al. 2006. *Cancer Res.* **66,** 9235.

Interested in Proteasome/Ubiquitination Research? *(continued...)*

UbcH8 Conjugating Enzyme, Human, Recombinant, *S. frugiperda*

Recombinant, human, UbcH8 conjugating enzyme. A member of the E2 family of ubiquitin conjugating enzymes and is similar in structure to UbcH7. It is specific for the conjugation of interferon-stimulated gene 15 (ISG15) to a variety of target proteins following stimulation with IFN-α or IFN-β. ISG15 conjugation then targets proteins for proteosomal degradation. UbcH8 is also known to associate with the Parkin protein and Staring, both of which are characterized as an E3 ubiquitin ligases. Binding to Parkin results in the activation of its ubiquitin ligase activity. Staring, which interacts with syntaxin-1, recruits UbcH8 to syntaxin-1, facilitating its ubiquitination and proteasome-mediated degradation. *Purity: ≥95% by SDS-PAGE.* M.W. 18,000

Cat. No. 662082 **100 µg** **€228**

Ref.: Kim, K.I., et al. 2004. *Mol. Cell. Biol.* **24,** 9592; Zhao, C., et al. 2004. *Proc. Natl. Acad. Sci. USA* **101,** 7578; Liu, M., et al. 2003. *J. Biol. Chem.* **278,** 1594; Tanaka, K., et al. 1998. *Mol. Cells* **8,** 503.

UbcH9 Conjugating Enzyme, Human, Recombinant, *S. frugiperda*

Recombinant, human UbcH9 conjugating enzyme. Interacts directly with proteins that are modified by SUMOylation and may be important for substrate recognition. A member of the E2 family of ubiquitin conjugating enzymes that is specific for the conjugation of SUMO-1, SUMO-2, and SUMO-3 to a variety of proteins including RanGAP1, IkBα and PML. *Purity: ≥98% by SDS-PAGE.* M.W. 20,000

Cat. No. 662083 **100 µg** **€228**

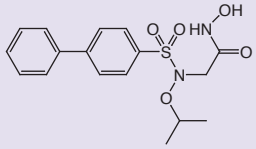
Ref.: Ito, K., et al. 2001. *Eur. J. Biochem.* **268,** 2725; Ito, K., et al. 1999. *Cytogenet. Cell. Genet.* **84,** 99; Kimura, M., et al. 1997. *Cytogenet. Cell. Genet.* **78,** 107.

NEW Matrix Metalloproteinase Inhibitors

MMP-2 Inhibitor III

((2-((Isopropoxy)-(1,1'-biphenyl-4-ylsulfonyl)-amino))-N-hydroxyacetamide)

A cell-permeable, potent, and Zn^{2+}-binding site-targeting inhibitor of MMP-2 (IC_{50} = 12 nM). Exhibits good selectivity over MMP-9 and MMP-3 (IC_{50} = 0.2 and 4.5 µM, respectively) and does not affect MMP-1 and MMP-7 (IC_{50} > 50 µM). *Purity: ≥97% by HPLC.* M.W. 364.4



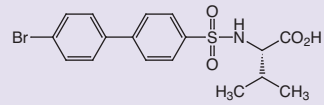
Cat. No. 444288 **5 mg** **€167**

Ref.: Tuccinardi, T., et al. 2006. *Bioorg. Med. Chem.* **14,** 4260; Rossello, A., et al. 2004. *Bioorg. Med. Chem.* **12,** 2441.

MMP-2/MMP-3 Inhibitor III, PD166793

((S)-2-(4'-Bromo-biphenyl-4-sulfonylamino-3-methylbutyric acid))

A cell-permeable, potent inhibitor of MMP-2, -3, and -13 (IC_{50} = 47, 12, and 8 nM, respectively) and a weaker inhibitor of MMP-1, -7, -9, and -14 (IC_{50} = 6.1, 7.2, 7.9, and 0.24 µM, respectively). Offers therapeutic benefits *in vivo* in various animal models of heart failure and diabetes. *Purity: ≥98% by TLC.* M.W. 412.3



Cat. No. 444284 **5 mg** **€111**

Ref.: Paolocci, N., et al. 2006. *J. Pharm. Exp. Ther.* **317,** 506; Zhou, Y.P., et al. 2005. *Diabetes* **54,** 2612; Peterson, J.T., et al. 2001. *Circulation* **103,** 2303; Spinale, F.G., et al. 1999. *Circ. Res.* **85,** 364.

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