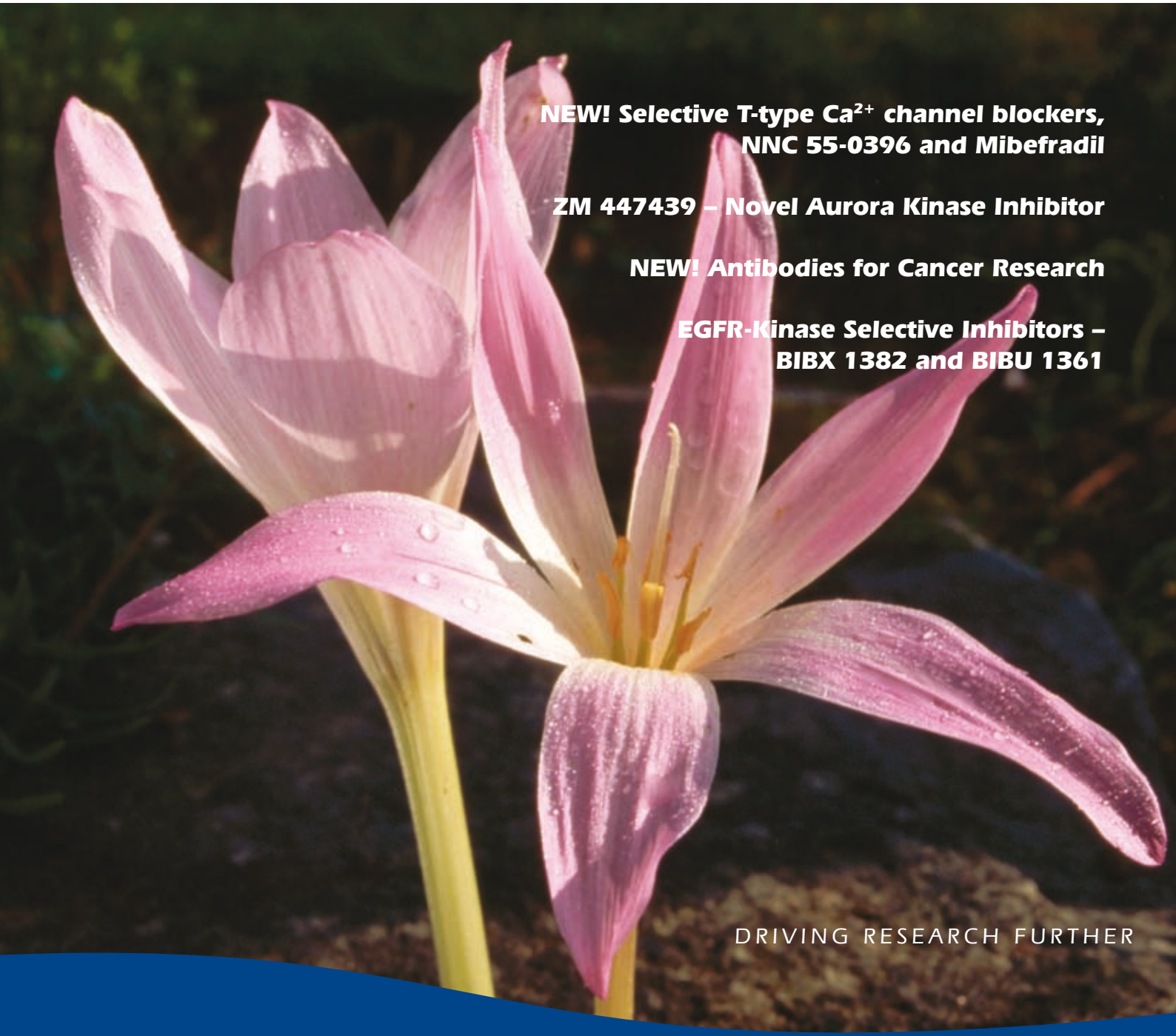
Signal Transduction

Product Guide | 2007

TOCRIS bioscience



NEW! Selective T-type Ca^{2+} channel blockers, NNC 55-0396 and Mibefradil

ZM 447439 – Novel Aurora Kinase Inhibitor

NEW! Antibodies for Cancer Research

EGFR-Kinase Selective Inhibitors – BIBX 1382 and BIBU 1361

DRIVING RESEARCH FURTHER

Neurochemicals | Signal Transduction Agents | Peptides | Biochemicals

Signal Transduction Product Guide

Cover photo

Colchicum autumnale: Autumn crocus

Origin of colchicine, an anti-inflammatory and anti-mitotic agent used to treat gout

Calcium Signaling Agents

Calcium Binding Protein Modulators

			Unit size
0378	A-7 HCl	Calmodulin antagonist	10 mg
1688	Autocamtide-2-related inhibitory peptide	Selective CaM kinase II inhibitor	1 mg
2090	CALP1	Cell-permeable calmodulin agonist	1 mg
2319	CALP2 New	Cell-permeable calmodulin antagonist	1 mg
2321	CALP3 New	Cell-permeable calmodulin agonist	1 mg
0953	Camstatin	Calmodulin antagonist	100 µg
1277	KN-62	CaM kinase II inhibitor	1 mg
1278	KN-93	CaM kinase II inhibitor	1 mg
1880	Mixed Kinase Inhibitor Tocriset	Selection of 5 mixed kinase inhibitors (Cat. Nos. 0741, 1277, 1288, 1289 and 1285)	1 set
0431	ML 9 HCl	Myosin light chain kinase inhibitor	10 mg 50 mg
1926	MLCK inhibitor peptide	Myosin light chain kinase inhibitor	1 mg
1885	MLCK inhibitor peptide 18	Selective inhibitor of myosin light chain kinase	1 mg
1551	STO-609 acetate	Selective CaM kinase kinase inhibitor	10 mg 50 mg
0368	W-5 HCl	Calmodulin antagonist	10 mg 50 mg
0369	W-7 HCl	Calmodulin antagonist	100 mg
0370	W-9 HCl	Calmodulin antagonist	10 mg 50 mg
0361	W-13 HCl	Calmodulin antagonist	10 mg 50 mg

Calcium ATPase Modulators

1236	BHQ	Inhibitor of SERCA ATPase	100 mg
1235	Cyclopiazonic Acid	Inhibitor of SERCA ATPase	10 mg 50 mg
1138	Thapsigargin	Potent inhibitor of SERCA ATPase	1 mg

Calcium Sensitive Protease Modulators

0448	Calpeptin	Calpain and cathepsin L inhibitor	10 mg 50 mg
1748	MG 132	Calpain and proteasome inhibitor	5 mg

General Calcium Signaling Agents

1234	A23187, free acid	Calcium ionophore	10 mg
0452	CCCP	Oxidative phosphorylation uncoupler	500 mg
1114	CGP 37157	Antagonist of mitochondrial Na^+/Ca^{2+} exchange	10 mg 50 mg
0507	Dantrolene, sodium salt	Ca^{2+} release inhibitor	100 mg
0839	DHBP	Ca^{2+} release inhibitor	100 mg
0453	FCCP	Oxidative phosphorylation uncoupler	10 mg 50 mg
1704	Ionomycin calcium salt	Calcium ionophore	1 mg
2092	Ionomycin free acid	Calcium ionophore	1 mg
1244	KB-R7943 mesylate	Na^+/Ca^{2+} exchange inhibitor (reverse mode)	10 mg 50 mg
0479	Malonoben	Oxidative phosphorylation uncoupler	10 mg 50 mg
1866	MRS 1845	Potent SOC inhibitor; blocks capacitative Ca^{2+} entry	10 mg 50 mg
1291	Ochratoxin A	Stimulates SERCA-ATP-dependent Ca^{2+} pump activity	1 mg
1439	Ruthenium Red	Inhibits ryanodine-sensitive Ca^{2+} release and mitochondrial uptake/release	100 mg
1329	Ryanodine	Ca^{2+} release inhibitor	5 mg
1147	SKF 96365 HCl	Inhibits receptor-mediated Ca^{2+} entry	10 mg 50 mg
2184	SN-6 New	Selective Na^+/Ca^{2+} exchange inhibitor (reverse mode)	10 mg 50 mg
1734	Tocriscreen Calcium Signaling	Collection of calcium signaling tools	1 set

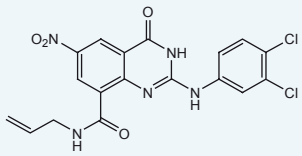
Cell Cycle and Apoptosis Reagents

Caspase Inhibitors/Activators/Substrates

			Unit size
2098	Apoptosis Activator 2	Promotes apoptosome formation and activates caspase-9/ caspase-3 pathway. Selectively induces tumor cell apoptosis	10 mg 50 mg
2172	AZ 10417808	Selective non-peptide caspase-3 inhibitor	10 mg 50 mg
2251	Cisplatin New	Potent proapoptotic anticancer agent; activates caspase-3	50 mg
1573	Ac-DEVD-AFC	Fluorogenic caspase substrate	5 mg
2166	Z-DEVD-FMK	Cell-permeable, irreversible caspase-3 inhibitor	1 mg
2168	Z-DQMD-FMK	Caspase-3 inhibitor	1 mg
1576	Ac-IEPD-AFC	Fluorogenic granzyme B substrate	5 mg
1574	Ac-IETD-AFC	Fluorogenic caspase substrate	5 mg
2170	Z-IETD-FMK	Caspase-8 inhibitor	1 mg
1575	Ac-LEHD-AFC	Fluorogenic caspase substrate	5 mg
2171	Z-LEHD-FMK	Cell-permeable caspase-9 inhibitor	1 mg
1758	PETCM	Activator of caspase-3	50 mg
2163	Z-VAD-FMK	Cell-permeable, irreversible caspase inhibitor	1 mg
2165	Z-VDVAD-FMK	Irreversible caspase-2 inhibitor	1 mg
2169	Z-VEID-FMK	Irreversible caspase-6 inhibitor	1 mg
2167	Z-WEHD-FMK	Caspase-5 inhibitor	1 mg
1572	Ac-YVAD-AFC	Fluorogenic caspase-1 (ICE) substrate	5 mg
2164	Z-YVAD-FMK	Caspase-1 (ICE) inhibitor	1 mg

AZ 10417808 – a non-peptide caspase-3 inhibitor

AZ 10417808 (Cat. No. 2172) is a member of a range of new aniloquinazones (AQZs) that are non-peptide caspase-3 inhibitors.



40-fold selective for caspase-3

In an enzyme assay, AZ 10417808 inhibits caspase-3 (measured as inhibition of substrate hydrolysis) with a K_i value of 247 nM. The inhibitor displays > 40-fold selectivity over caspases-1, -2, -6, -7 and -8 (see table below).

Anti-apoptotic in whole cells

AZ 10417808 dose-dependently and completely blocks staurosporine-induced intracellular DEVDase activity in SH-SY5Y cells (IC_{50} = 14.9 μM). AZ 10417808 produces anti-apoptotic effects: SH-SY5Y cell viability is 92% in cells treated with 1 μM staurosporine/10 μM AZ 10417808, as opposed to 64% in cells treated with staurosporine alone.

Scott *et al* (2003) Novel small molecule inhibitors of caspase-3 block cellular and biochemical features of apoptosis. J.Pharmacol.Exp.Ther. ***304*** 433.

(Sold with the permission of AstraZeneca UK Ltd)

	Caspase-1	Caspase-2	**Caspase-3**	Caspase-6	Caspase-7	Caspase-8
AZ 10417808	> 10 μM	> 10 μM	**247 nM**	> 10 μM	> 10 μM	> 10 μM

K_i values for caspase inhibition by AZ 10417808. Data taken from Scott *et al* (2003).

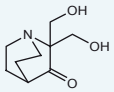
Other

1515	17-AAG	Selective Hsp90 inhibitor	500 μg
1229	Actinomycin D	Antineoplastic antibiotic	10 mg
0788	3-Aminobenzamide	PARP inhibitor	100 mg
1290	Anisomycin	Protein synthesis inhibitor	10 mg 50 mg
1954	Antagonist G New	Antiproliferative agent; broad spectrum neuropeptide receptor antagonist	1 mg
1227	Apigenin	Anticancer agent	10 mg 50 mg
1777	Arctigenin	Inhibitor of IκBα phosphorylation. Antiviral, antiproliferative agent	10 mg 50 mg
1761	Baicalein	Induces G1 and G2 cell cycle arrest. Also lipoxygenase inhibitor	50 mg
2160	Bax channel blocker	Inhibits Bax-mediated mitochondrial cytochrome *c* release	10 mg 50 mg
1786	Bax inhibitor peptide P5	Inhibitor of Bax-mediated apoptosis	1 mg
1785	Bax inhibitor peptide V5	Inhibitor of Bax-mediated apoptosis	1 mg
1787	Bax inhibitor peptide, negative control	Negative control peptide for Cat. Nos. 1785 and 1786	1 mg

Other Cell Cycle and Apoptosis Reagents continued

			Unit size
1743	Bay 11-7085	Irreversible inhibitor of TNF-α-induced IκBα phosphorylation. Stimulates apoptosis	10 mg
1744	Bay 11-7821	Irreversible inhibitor of TNF-α-induced IκBα phosphorylation. Stimulates apoptosis	10 mg
1760	(±)-Blebbistatin	Selective inhibitor of nonmuscle myosin II	10 mg
1853	(*R*)-(+)-Blebbistatin	Inactive enantiomer of Cat. No. 1760	1 mg
1852	(*S*)-(-)-Blebbistatin	Selective inhibitor of nonmuscle myosin II ATPase activity. Active enantiomer	1 mg
1231	Brefeldin A	Disrupts protein translocation to Golgi	5 mg
1100	Camptothecin	DNA topoisomerase inhibitor	25 mg 100 mg
2251	Cisplatin New	DNA-alkylating antitumor agent	50 mg
1364	Colchicine	Inhibitor of tubulin	1 g
2294	Cordycepin New	Anticancer and antifungal agent	10 mg
0970	Cycloheximide	Inhibitor of protein synthesis	100 mg
1233	Cytochalasin D	Disrupts actin filament function	1 mg 5 mg
1643	D-64131	Inhibitor of tubulin polymerization. Antitumor *in vivo*	10 mg 50 mg
1417	Daidzein	Arrests cell cycle in G1 phase	50 mg
1467	Daunorubicin HCl	Anticancer agent	10 mg
2137	2,3-DCPE HCl	Selectively induces cancer cell apoptosis	10 mg 50 mg
1770	Deguelin	Anticancer and antiviral agent; chemopreventive and proapoptotic	10 mg
2145	Difopein	High affinity inhibitor of 14-3-3 proteins; induces apoptosis	100 µg
2252	Doxorubicin HCl New	Antitumor antibiotic agent. Inhibits DNA topoisomerase II	10 mg 50 mg
2156	Embelin	Inhibitor of X-linked inhibitor of apoptosis (XIAP); cell-permeable and antitumor	10 mg 50 mg
1226	Etoposide	Topoisomerase II inhibitor	100 mg
1850	Exo1	Inhibits Golgi-ER traffic; blocks exocytosis	10 mg 50 mg
2226	Flutax 1 New	Fluorescent taxol derivative	1 mg
1768	Fumagillin New	Antibiotic, antiangiogenic and antitumor agent. Inhibits methionine aminopeptidase-2	1 mg
1368	Geldanamycin	Selective Hsp90 inhibitor	1 mg
1964	Gossypol	Anticancer, antifertility agent	50 mg
1541	HA14-1	Bcl-2 inhibitor. Induces apoptosis	10 mg 50 mg
1416	Homoharringtonine	Inhibitor of protein synthesis. Antileukemic agent	10 mg
2192	4-HQN New	PARP inhibitor	50 mg
1520	Hypericin	Photosensitive antiviral and anticancer agent	1 mg
1813	Indirubin-3´-oxime	Induces cell cycle arrest, antiproliferative	10 mg 50 mg

PRIMA-1 – restores mutant p53 activity

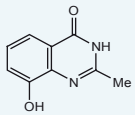


The tumor suppressor p53 inhibits tumor growth via cell-cycle arrest and the induction of apoptosis. Tumors carrying mutations in p53 are often more resistant to chemotherapy than those carrying wild-type p53. The novel compound PRIMA-1 (Cat. No. 1862) selectively restores sequence-specific DNA binding, wild-type conformation and transcriptional transactivation function to mutant p53. It induces p53-dependent apoptosis and *in vivo* PRIMA-1 suppresses the growth of human tumor xenografts carrying mutant p53.

Bykov *et al* (2002) Restoration of the tumour suppressor function to mutant p53 by a low-molecular-weight compound. Nature Med. ***8*** 282. **Bykov** *et al* (2002) Mutant p53-dependent growth suppression distinguishes PRIMA-1 from known anticancer drugs: a statistical analysis of information in the National Cancer Institute database. Carcinogenesis ***23*** 2011.

Other Cell Cycle and Apoptosis Reagents continued

Potent PARP inhibitor, NU 1025



NU 1025 (Cat. No. 1401) is a potent inhibitor of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) that is reported to be 50-fold more effective than 3-aminobenzamide. NU 1025 displays an IC_{50} of 400 nM for PARP inhibition. *In vitro*, the compound potentiates the growth inhibition and cytotoxicity of various anticancer agents in tumor cells. In studies with murine leukemia L1210 cells, NU 0125 (200 μM) enhances the action of both the DNA-methylating agent MTIC and ionizing radiation 3.5- and 1.4-fold, respectively, at the 10% survival level.

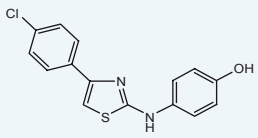
Griffin *et al* (1998) Resistance-modifying agents. 5. Synthesis and biological properties of quinazolinone inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP). J.Med.Chem. ***41*** 5247. **Bowman** *et al* (1998) Potentiation of anti-cancer agent cytotoxicity by the potent poly(ADP-ribose) polymerase inhibitors NU1025 and NU1064. Br.J.Cancer. ***78*** 1269. **Delaney** *et al* (2000) Potentiation of temozolomide and topotecan growth inhibition and cytotoxicity by novel poly(adenosine diphosphoribose) polymerase inhibitors in a panel of human tumor cell lines. Clin.Cancer.Res. ***6*** 2860.

			Unit size
1803	ITE	Endogenous agonist for the transcription factor aryl hydrocarbon receptor	10 mg
1989	c-JUN peptide	JNK/c-Jun interaction inhibitor; induces tumor cell apoptosis	1 mg
2228	Leflunomide New	Immunosuppressant	50 mg
1987	Leptomycin B	Inhibits nuclear export of proteins; antitumor	5 μg
1461	Linomide	Immunomodulator with antitumor properties	10 mg
			50 mg
1646	Lonidamine	Anticancer and antispermatogenic agent. Inhibits mitochondrial hexokinase	10 mg
			50 mg
1530	Lovastatin	HMG-CoA reductase inhibitor. Induces apoptosis	10 mg
			50 mg
1230	Methotrexate	Cytotoxic agent	100 mg
1807	2-Methoxyestradiol	Apoptotic and antiangiogenic agent	10 mg
			50 mg
2377	Anti-MDM2 Y New	Antibody recognizing MDM2	100 μg
2381	Anti-phospho-MDM2 (Ser^{186}) Y New	Antibody recognizing MDM2 phosphorylated at Ser^{186}	100 μg
1526	Mevastatin	HMG-CoA reductase inhibitor. Induces apoptosis	10 mg
			50 mg
1489	Mithramycin A	Anticancer antibiotic	1 mg
1305	Monastrol	Selective inhibitor of mitotic kinesin Eg5	10 mg
			50 mg
2360	Anti-N-Myc Y New	Antibody recognizing N-Myc	100 μg
1505	Mycophenolic acid	Immunosuppressant	100 mg
1228	Nocodazole	Microtubule inhibitor	10 mg
1697	Noscapine HCl	Tubulin inhibitor; induces apoptosis	100 mg
1547	NSC 95397	Cdc25 dual phosphatase inhibitor. Blocks G2/M phase transition	10 mg
			50 mg
2185	NSC 146109 HCl New	Cell-permeable, genotype-selective anti-tumor agent; activates p53-dependent transcription	10 mg
			50 mg
1867	NSC 663284 New	Cdc25 phosphatase inhibitor; blocks tumor cell proliferation	10 mg
2087	NTR 368	p75NTR fragment; induces apoptosis	1 mg
1401	NU 1025	Potent PARP inhibitor	10 mg
			50 mg
2067	187-1, N-WASP inhibitor	Inhibits actin assembly	1 mg
2366	Anti-$p14^{ARF}$ Y New	Antibody recognizing $p14^{ARF}$	100 μg
2369	Anti-p53 Y New	Antibody recognizing p53	100 μg
2375	Anti-p53 Y New	Antibody recognizing p53	100 μg
2376	Anti-p53 Y New	Antibody recognizing p53	100 μg
2378	Anti-p53 Y New	Antibody recognizing p53	100 μg
1554	Piceatannol	Antiproliferative, anti-inflammatory and immunomodulatory	10 mg
1267	Pifithrin-α HBr	p53 inhibitor	10 mg
			50 mg

Other Cell Cycle and Apoptosis Reagents continued

Sphingosine kinase-selective inhibitor, SKI II

SKI II (Cat. No. 2097) is a selective non-lipid inhibitor of sphingosine kinase (IC_{50} = 0.5 μM) that does not act at the ATP-binding site. The compound displays no inhibition of ERK2,



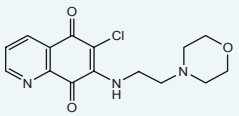
PI 3-kinase, or PKCα at concentrations up to 60 μM. It reduces levels of sphingosine-1-phosphate in MDA-MB-231 breast cancer cells, and induces apoptosis and inhibits proliferation in several tumor cell lines *in vitro* (IC_{50} = 0.9-4.6 μM).

French *et al* (2003) Discovery and evaluation of inhibitors of human sphingosine kinase. Cancer Res. ***63*** 5862.

			Unit size
1862	PRIMA-1	Restores mutant p53 activity; induces apoptosis	10 mg
			50 mg
2144	R18	Inhibitor of 14-3-3 proteins; induces apoptosis	1 mg
1589	Radicicol	Hsp90 inhibitor. Antifungal antibiotic	1 mg
1292	Rapamycin	Immunosuppressant	1 mg
1418	Resveratrol	Anti-tumor and anti-oxidant agent	100 mg
2097	SKI II New	Selective non-lipid inhibitor of sphingosine kinase; displays antitumor properties	10 mg
			50 mg
1542	Splitomicin	Histone deacetylase (Sir2p) inhibitor	10 mg
			50 mg
1621	Streptozocin	DNA alkylator; antitumor and induces diabetes	100 mg
			500 mg
1946	[D-Arg[1],D-Phe[5],D-Trp[7,9],Leu[11]]-Substance P	Induces apoptosis in cancer cells *in vitro*. Broad spectrum neuropeptide receptor antagonist/inverse agonist	1 mg
1707	Sulindac	Prodrug of anticancer agents sulindac sulfide and sulfone	100 mg
1472	Suramin hexasodium salt	Anticancer and antiviral agent	100 mg
1097	Taxol	Promotes assembly and inhibits disassembly of microtubules	10 mg
			50 mg
1567	Thiolutin	Antibiotic. Inhibits vitronectin cell adhesion	1 mg
1509	TMS	Inhibits cancer cell growth. Cytochrome P450 1B1 inhibitor	10 mg
			50 mg
1738	Tocriscreen Cell Cycle and Apoptosis	Collection of cell cycle and apoptosis tools	1 set
1406	Trichostatin A	Potent, selective histone deacetylase inhibitor	1 mg
2191	*S*-Trityl-L-cysteine New	Potent, selective inhibitor of mitotic kinesin Eg5	50 mg
1256	Vinblastine sulfate	Disrupts microtubules	10 mg
			50 mg
1257	Vincristine sulfate	Disrupts microtubules	10 mg
			50 mg
2458	ZM 447439 New	Inhibits Aurora mitotic protein kinases A and B	10 mg

NSC 663284 – selective Cdc25 phosphatase inhibitor

NSC 663284 (Cat. No. 1867) is a potent and selective inhibitor of Cdc25 dual-specificity phosphatases. K_i values are 29, 95 and 89 nM for human Cdc25A, $Cdc25B_2$ and Cdc25C respectively. The inhibitor displays > 20- and > 450-fold selectivity for Cdc25 over VHR and PTP1B phosphatases respectively. NSC 663284



arrests cells at both G1 and G2/M phases and inhibits cdk2 and cdk1 activation. It blocks proliferation of a range of human tumor cell lines (IC_{50} = 0.2-35 μM).

Lazo *et al* (2001) Discovery and biological evaluation of a new family of potent inhibitors of the dual specificity protein phosphatase Cdc25. J.Med.Chem. ***44*** 4042. **Pu** *et al* (2002) Dual G1 and G2 phase inhibition by a novel, selective Cdc25 inhibitor 7-chloro-6-(2-morpholin-4-ylethylamino)-quinoline-5,8-dione. J.Biol.Chem. ***277*** 46877. **Han** *et al* (2004) NAD(P)H:Quinone oxidoreductase-1-dependent and -independent cytotoxicity of potent quinine Cdc25 phosphatase inhibitors. J.Pharmacol.Exp.Ther. ***309*** 64.

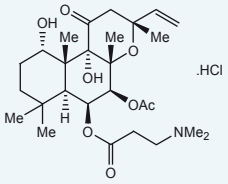
Cyclic Nucleotide Related Tools

Adenylyl Cyclase/Guanylyl Cyclase Modulators

			Unit size
1099	Forskolin	Adenylyl cyclase activator	10 mg
			50 mg
1898	Guanylin (human)	Endogenous activator of intestinal guanylyl cyclase	500 µg
1603	NKH 477	Water-soluble adenylyl cyclase activator	10 mg
			50 mg
0880	ODQ	Selective inhibitor of NO-sensitive guanylyl cyclase	10 mg
			50 mg
1183	PACAP 1-27	Potent stimulator of adenylyl cyclase	100 µg
1186	PACAP 1-38	Potent stimulator of adenylyl cyclase	100 µg
1882	PKA Tocriset	Selection of 5 PKA modulators (Cat. Nos. 1337, 1140, 1099 1288 and 1603)	1 set
0756	SIN-1 chloride	Guanylyl cyclase activator	50 mg
0746	Zinc protoporphyrin IX	Guanylyl cyclase inhibitor. Also inhibits heme oxygenase	10 mg
			50 mg

Water-soluble forskolin derivative – NKH 477

NKH 477 (colforsin dapropate hydrochloride) (Cat. No. 1603) is a novel water-soluble analog of forskolin (Cat. No. 1099) that is a potent adenylyl cyclase activator, both *in vitro* and *in vivo*.



Activity *in vitro*

NKH 477 displays some selectivity for the cardiac (type V) adenylyl cyclase, activating it more potently than forskolin, and to a greater extent than either type II or type III adenylyl cyclase. In isolated guinea pig trachea, NKH 477 potently induces relaxation (EC_{50} = 32.6 nM).

Orally active *in vivo*

NKH 477 has potent cardiovascular effects *in vivo*, increasing heart rate and decreasing blood pressure in dogs following either oral or intravenous administration.

The availability of this new orally-active water-soluble adenylyl cyclase activator should aid the study of adenylyl cyclase activity *in vitro* and *in vivo*.

Hosono *et al* (1992) Cardiovascular and adenylate cyclase stimulant properties of NKH477, a novel water-soluble forskolin derivative. J.Cardiovasc.Pharmacol. ***19*** 625. **Satake** *et al* (1998) Relaxant effects of NKH477, a new water-soluble forskolin derivative, on guinea-pig tracheal smooth muscle: the role of Ca^{2+}-activated K^+ channels. Br.J.Pharmacol. ***123*** 753. **Toya** *et al* (1998) Forskolin derivatives with increased selectivity for cardiac adenylyl cyclase. J.Mol.Cell.Cardiol. ***30*** 97.

Phosphodiesterase Inhibitors

2237	BRL 50481 New	Selective PDE7 inhibitor	10 mg
			50 mg
0915	Cilostamide	PDE3 inhibitor	10 mg
			50 mg
1692	Cilostazol	PDE3A inhibitor. Also adenosine uptake inhibitor	10 mg
0691	Dipyridamole	PDE5/6/8/10 inhibitor	500 mg
1261	EHNA HCl	PDE2 inhibitor	10 mg
			50 mg
0438	Etazolate HCl	PDE4 inhibitor	10 mg
			50 mg
1694	Ibudilast	PDE inhibitor (non-selective)	10 mg
1816	ICI 63197	PDE4 inhibitor	10 mg
			50 mg
1504	Milrinone	PDE3 inhibitor	10 mg
			50 mg
0552	MMPX	PDE1 inhibitor	10 mg
			50 mg
0432	MY-5445	PDE5 inhibitor	10 mg
			50 mg
1881	Phosphodiesterase Inhibitor Tocriset	Selection of 5 phosphodiesterase inhibitors (Cat. Nos. 0915, 1504, 0415, 1349 and 1046)	1 set
0415	Ro 20-1724	PDE4 inhibitor	50 mg
0905	Rolipram	PDE4 inhibitor	10 mg
			50 mg
1349	(*R*)-(-)-Rolipram	More active enantiomer of Cat. No. 0905	10 mg
			50 mg
1350	(*S*)-(+)-Rolipram	Less active enantiomer of Cat. No. 0905	10 mg
			50 mg

Phosphodiesterase Inhibitors continued

			Unit size
1148	Siguazodan	PDE3 inhibitor	10 mg
			50 mg
1676	T 0156 HCl	Highly potent, selective PDE5 inhibitor	10 mg
			50 mg
2337	Trequinsin HCl New	Ultrapotent inhibitor of cAMP-phosphodiesterase	10 mg
0757	Vinpocetine	PDE1 inhibitor	50 mg
1821	YM 976	PDE4 inhibitor	10 mg
			50 mg
0947	Zaprinast	PDE5/6/9 inhibitor	25 mg
1046	Zardaverine	PDE3/4 inhibitor	10 mg
			50 mg

Characteristics of Phosphodiesterases

Isoenzyme Family	Characteristics	Physiological Effects of Inhibitors	Inhibitor	Cat. No.	IC_{50} (µM)
PDE1	Ca^{2+}-calmodulin dependent, cAMP specific	Vascular smooth muscle relaxation, central actions	MMPX Vinpocetine	0552 0757	5.2[1] 21[2]
PDE2	cAMP hydrolytic activity stimulated by cGMP	Potentiation of inhibition of platelet aggregation, inhibition of hypoxic pressor response	EHNA	1261	1.0[3]
PDE3	cAMP hydrolytic activity inhibited by cGMP	Positive inotropism, smooth muscle relaxation, platelet aggregation, lipolysis stimulation	Cilostamide Cilostazol Siguazodan Zardaverine	0915 1692 1148 1046	0.07[4] 0.2 (PDE3A)[5] 0.12[4] 0.5[6]
PDE4	cAMP specific	Airway smooth muscle relaxation, inhibition of inflammatory responses, gastric acid secretion, central effects	Etazolate Ro 20-1724 Rolipram YM 976 Zardaverine	0438 0415 0905 1821 1046	2.0[7] 2.0[8] 2.0[8] 0.0022[9] 0.8[6]
PDE5	cGMP specific	Inhibition of platelet aggregation	Dipyridamole MY-5445 T 0156 Zaprinast	0691 0432 1676 0947	0.9[3] 0.5[10] 0.00023[11] 0.76[3]
PDE6	Photoreceptor cGMP specific	Modulation of visual transduction	Dipyridamole Zaprinast	0691 0947	0.38[8] 0.15[8]
PDE7	High specificity for cAMP, rolipram insensitive	Unknown	BRL 50481	2237	0.26[13]
PDE8	Specific for cAMP hydrolysis, IBMX insensitive	Unknown	Dipyridamole	0691	4.5[8]
PDE9	cGMP specific, lowest K_m yet reported for cGMP	Unknown	Zaprinast	0947	29.0[3]
PDE10	cAMP and cAMP-inhibited cGMP PDE	Unknown	Dipyridamole	0691	0.45-1.2[12]

1. **Wells and Miller** (1988) Methods Enzymol. ***159*** 489. 2. **Hagiwara** *et al* (1984) Biochem.Pharmacol. ***33*** 453. 3. **Soderling** *et al* (1998) J.Biol.Chem. ***273*** 15553. 4. **Tang** *et al* (1994) Eur.J.Pharmacol. ***268*** 105. 5. **Schror** (2002) Diabetes Obes.Metab. ***4*** S14. 6. **Galvin and Schudt** (1990) Naunyn-Schmied.Arch.Pharmacol. ***342*** 221. 7. **Ahluwalia and Rhoads** (1982) Biochem.Pharmacol. ***31*** 665. 8. **Soderling** *et al* (1998) Proc.Natl.Acad.Sci.USA ***95*** 8991. 9. **Aoki** *et al* (2000) J.Pharmacol.Exp.Ther. ***295*** 255. 10. **Hidaka and Endo** (1984) Adv.Cyclic Nucleotide Res. ***16*** 245. 11. **Mochida** *et al* (2002) Eur.J.Pharmacol. ***456*** 91. 12. **Fujisgige** *et al* (1999) J.Biol.Chem. ***274*** 18438. 13. **Smith** *et al* (2004) Mol.Pharmacol. ***66*** 1679.

Protein Kinase A Reagents

1337	cAMPS-Rp, triethylammonium salt	cAMP antagonist	1 mg
1333	cAMPS-Sp, triethylammonium salt	Cell-permeable cAMP analog	1 mg
1140	8-Bromo-cAMP, sodium salt	Cell-permeable cAMP analog	10 mg
			50 mg
1141	Dibutyryl-cAMP, sodium salt	Cell-permeable cAMP analog	10 mg
			50 mg
1288	KT 5720	Selective protein kinase A inhibitor	100 µg
1882	PKA Tocriset	Selection of 5 PKA modulators (Cat. Nos. 1337, 1140, 1099, 1288 and 1603)	1 set
1344	SAMS Peptide	AMP-activated protein kinase substrate	500 µg

Other

1645	8CPT-2Me-cAMP, sodium salt	Selective Epac activator	1 mg
1735	Tocriscreen Cyclic Nucleotide Tools	Collection of cyclic nucleotide tools	1 set

Cytokine Signaling Agents

			Unit size
1793	AF 12198	Potent, selective human type I IL-1 receptor antagonist	1 mg
1777	Arctigenin	Inhibitor of IκBα phosphorylation. Also inhibits MKK1	10 mg
			50 mg
2446	AS 101 New	Immunomodulator; inhibits IL-10 synthesis and potentiates IL-1α, IL-2 and TNFα release	10 mg
			50 mg
1743	Bay 11-7085	Irreversible inhibitor of TNF-α-induced IκBα phosphorylation	10 mg
1744	Bay 11-7821	Irreversible inhibitor of TNF-α-induced IκBα phosphorylation	10 mg
1798	Gabexate mesylate	Inhibits TNF-α production. Also antithrombotic agent	10 mg
			50 mg
2265	Lyn peptide inhibitor New	Inhibits Lyn-dependent activities of IL-5 receptor; cell-permeable	1 mg
1748	MG 132	Inhibits NF-κB activation; proteasome and calpain inhibitor	5 mg
1093	Pirfenidone	Antifibrotic agent; regulates cytokine levels *in vivo*	10 mg
			50 mg
1947	PR 39 (porcine)	IκBα inhibitor	500 µg
0727	Pyrrolidinedithiocarbamate ammonium	Inhibits NF-κB, prevents increase in NOS mRNA	50 mg
1794	Ro 26-4550 trifluoroacetate New	Competitive inhibitor of IL-2/IL-2Rα receptor interaction	10 mg
1778	Ro 106-9920	Inhibitor of NF-κB activation	10 mg
			50 mg
2089	RS 102895 New	CCR2b chemokine receptor antagonist	10 mg
			50 mg
2008	SKF 86002 2HCl New	Inhibits human monocyte IL-1 and TNF-α production; p38 MAP kinase inhibitor	10 mg
			50 mg
0652	Thalidomide	TNF-α synthesis inhibitor	100 mg
1675	YM 90709	Interleukin-5 receptor antagonist	10 mg

Enzyme Inhibitors/Substrates/Activators

Enzyme Inhibitors

Aldose Reductase Inhibitors

0485	Alrestatin	Aldose reductase inhibitor	10 mg
			50 mg
0518	EBPC	Aldose reductase inhibitor	10 mg
			50 mg
0847	Statil	Aldose reductase inhibitor	100 mg

ATPase Modulators

1283	ARL 67156	Ecto-ATPase inhibitor	10 mg
1334	Bafilomycin A1	H^+-ATPase (vacuolar) inhibitor	10 µg
1236	BHQ	Inhibitor of SERCA ATPase	100 mg
1760	(±)-Blebbistatin	Selective inhibitor of non-muscle myosin II ATPase activity	10 mg
1853	(*R*)-(+)-Blebbistatin New	Inactive enantiomer of Cat. No. 1760	1 mg
1852	(*S*)-(-)-Blebbistatin New	Selective inhibitor of nonmuscle myosin II ATPase activity. Active enantiomer	1 mg
1870	BTS	Selective inhibitor of skeletal muscle myosin II ATPase activity	10 mg
1235	Cyclopiazonic Acid	Inhibitor of SERCA ATPase	10 mg
			50 mg
1076	Ouabain	Na^+,K^+-ATPase inhibitor	100 mg
2006	Paxilline	SERCA ATPase blocker. Also potent BK_{Ca} channel blocker	10 mg
1690	SCH 28080	H^+, K^+-ATPase inhibitor	10 mg
			50 mg
1138	Thapsigargin	Potent inhibitor of SERCA ATPase	1 mg

Cyclooxygenase Inhibitors

			Unit size
1706	Acetaminophen	Cyclooxygenase inhibitor; may be selective for COX-3	100 mg
1430	DuP 697	Cyclooxygenase (COX-2) inhibitor	10 mg
			50 mg
1769	Flurbiprofen	Cyclooxygenase inhibitor	100 mg
1507	FR 122047 HCl	Cyclooxygenase (COX-1) inhibitor	10 mg
			50 mg
1708	Indomethacin	Cyclooxygenase inhibitor (COX-1 > COX-2)	100 mg
0960	Piroxicam	Cyclooxygenase (COX-1) inhibitor	100 mg
1418	Resveratrol	Cyclooxygenase inhibitor	100 mg
1707	Sulindac	Cyclooxygenase inhibitor (following metabolism to sulindac sulfide)	100 mg

GTPase Modulators

1774	Dynamin inhibitory peptide	Dynamin inhibitor	1 mg
1775	Dynamin inhibitory peptide, myristoylated	Cell-permeable dynamin inhibitor	1 mg
1776	Dynamin inhibitory peptide, myristoylated (control)	Control peptide version of Cat. Nos. 1774 and 1775	1 mg

Histone Deacetylase Inhibitors

2421	Scriptaid New	Histone deacetylase inhibitor	10 mg
			50 mg
1542	Splitomicin	Histone deacetylase (Sir2p) inhibitor	10 mg
			50 mg
1406	Trichostatin A	Histone deacetylase inhibitor	1 mg

HMG-CoA Reductase Inhibitors

1530	Lovastatin	HMG-CoA reductase inhibitor	10 mg
			50 mg
1526	Mevastatin	HMG-CoA reductase inhibitor	10 mg
			50 mg
2318	Pravastatin sodium salt New	HMG-CoA reductase inhibitor; water-soluble	50 mg
1965	Simvastatin	HMG-CoA reductase inhibitor	50 mg

Monoamine Oxidase Inhibitors

0767	Bifemelane	MAO-A and MAO-B inhibitor	10 mg
			50 mg
1095	(*R*)-(-)-Deprenyl HCl	MAO-B inhibitor	1 g
1132	Harmane HCl	MAO-A and MAO-B inhibitor	100 mg
0724	Pirlindole mesylate	MAO-A inhibitor	10 mg
			50 mg
0723	Tetrindole mesylate	MAO-A inhibitor	10 mg
			50 mg

Protease Inhibitors

0384	*N*-Acetyl-L-leucyl-L-leucyl-L-methional	Cathepsin inhibitor	10 mg
			50 mg
0448	Calpeptin	Calpain and cathepsin L inhibitor	10 mg
			50 mg
0442	4-Chlorophenylguanidine HCl	Urokinase inhibitor	100 mg
1959	GW 311616 HCl	Potent, selective human neutrophil elastase inhibitor	10 mg
2267	Lactacystin New	Cell-permeable, potent and selective proteasome inhibitor	200 µg
1167	Leupeptin hemisulfate	Inhibits trypsin-like/cysteine proteases	25 mg
1748	MG 132	Proteasome and calpain inhibitor. Inhibits NF-κB activation	5 mg
1190	Pepstatin A	Aspartic protease inhibitor	25 mg

Other Enzyme Inhibitors

			Unit size
2372	ABT 702 2HCl New	Potent adenosine kinase inhibitor; orally active	10 mg
2227	CI 976 New	Acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor	10 mg
			50 mg
1261	EHNA HCl	Adenosine deaminase inhibitor	10 mg
			50 mg
1956	Bestatin	Aminopeptidase inhibitor	10 mg
0455	(*S*)-(-)-Carbidopa	Aromatic L-amino acid decarboxylase inhibitor	25 mg
			100 mg
0584	L-(-)-α-Methyldopa	Aromatic L-amino acid decarboxylase inhibitor	1 g
0483	OR-486	Catechol-O-methyl transferase inhibitor	50 mg
1323	Butabindide oxalate	CCK-inactivating serine peptidase inhibitor	10 mg
			50 mg
1484	Oleylethanolamide	Ceramidase inhibitor	10 mg
			50 mg
1719	Tocriscreen Enzyme Inhibitors	Collection of enzyme inhibitors	1 set
1103	Ketoconazole	Cytochrome P450c17 inhibitor	100 mg
1509	TMS	Cytochrome P450 1B1 inhibitor	10 mg
			50 mg
1639	AY 9944 2HCl	Δ^7-Dehydrocholesterol reductase inhibitor. Also inhibits hedgehog (hh) signaling	10 mg
0650	Trimethoprim	Dihydrofolate reductase inhibitor	1 g
1258	1-Deoxynojirimycin	Glucosidase I and II inhibitor	5 mg
			25 mg
0759	Castanospermine	Glucosidases α and β inhibitor	10 mg
			50 mg
0747	Tin protoporphyrin IX dichloride	Heme oxygenase inhibitor	10 mg
			50 mg
0746	Zinc protoporphyrin IX	Heme oxygenase and guanylyl cyclase inhibitor	10 mg
			50 mg
0512	SKF 91488 2HCl	Histamine *N*-methyltransferase inhibitor	10 mg
			50 mg
0607	17-ODYA	LTB-ω-Hydroxylase inhibitor	10 mg
			50 mg
1259	1-Deoxymannojirimycin HCl	α-Mannosidase I inhibitor	5 mg
			25 mg
1768	Fumagillin New	Methionine aminopeptidase-2 inhibitor	1 mg
1646	Lonidamine	Mitochondrial hexokinase inhibitor	10 mg
			50 mg
0500	N^1,N^{12}-Diethylspermine 4HCl	Polyamine synthase inhibitor	10 mg
			50 mg
1634	Y-29794 oxalate	Prolyl endopeptidase inhibitor	10 mg
			50 mg
0652	Thalidomide	TNF-α synthesis inhibitor	100 mg
1510	Ozagrel HCl	Thromboxane A_2 synthetase inhibitor	10 mg
			50 mg
0938	*p*-Chlorophenylalanine	Tryptophan hydroxylase inhibitor	100 mg
0478	Flurofamide	Urease inhibitor	50 mg

Enzyme Substrates/Activators

0357	*N*-Acetyltryptamine	Substrate for serotonin *N*-acetyl transferase	10 mg
			50 mg
2422	AKTide-2T New	Akt/PKB substrate (synthetic)	1 mg
1353	Akt/SKG Substrate Peptide	Akt/PKB substrate (synthetic)	1 mg
1892	Amyloid β-Peptide (10-20) (human)	MMP-2/gelatinase A/type IV collagenase substrate	1 mg
1802	2B-(SP)	Selective GSK-3 phosphopeptide substrate	1 mg
1458	DAPK Substrate Peptide	Death associated protein kinase substrate (synthetic)	1 mg
0468	N^1,N^{11}-Diethylnorspermine 4HCl	Spermine and spermidine acetyltransferase potentiator	10 mg
			50 mg
1764	Hemopressin	Bioactive substrate for endopeptidase 24.15, neurolysin and ACE	1 mg
1352	Phospho-Glycogen Synthase Peptide-2 (substrate)	Glycogen synthase kinase-3 substrate (synthetic)	500 µg
1155	RR-src	Tyrosine kinase substrate peptide	1 mg
1344	SAMS Peptide	AMP-activated protein kinase substrate	500 µg

Glycobiology Agents

			Unit size
0485	Alrestatin	Aldose reductase inhibitor	10 mg
			50 mg
0759	Castanospermine	Glucosidases α and β inhibitor	10 mg
			50 mg
1259	1-Deoxymannojirimycin HCl	α-Mannosidase I inhibitor	5 mg
			25 mg
1258	1-Deoxynojirimycin	Glucosidase I and II inhibitor	5 mg
			25 mg
0518	EBPC	Aldose reductase inhibitor	10 mg
			50 mg
1805	Gly-Pro-Arg-Pro	Inhibits fibrin polymerization	5 mg
1263	GR 144053 3HCl	Fibrinogen (glycoprotein IIb/IIIa) receptor antagonist. Antithrombotic	10 mg
			50 mg
1903	Peptide F9	Inhibits laminin-mediated cell adhesion and migration	1 mg
0847	Statil	Aldose reductase inhibitor	100 mg

G Protein Reagents

Selective inhibitors of Rac1-GEF interaction

Rac1 inhibitor peptides

The Rho GTPase Rac1 is specifically activated by several guanine nucleotide exchange factors (GEFs) such as Trio, GEF-H1 and Tiam1. These GEFs do not activate the closely related GTPase Cdc42 and the specificity is governed by the Rac1-GEF binding interaction. The residue tryptophan 56 (W56) in the GEF-binding domain of Rac1 appears to be the key determinant of this specificity, as the introduction of W56 to Cdc42 renders it responsive to Rac1-specific GEFs.

Met-Val-Asp-Gly-Lys-Pro-Val-Asn-Leu-Gly-Leu-Trp-Asp-Thr-Ala-Gly

Rac1 Inhibitor W56 (Cat. No. 2221)

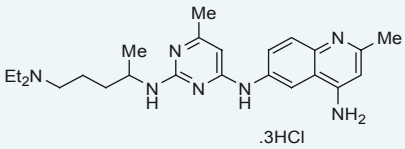
Met-Val-Asp-Gly-Lys-Pro-Val-Asn-Leu-Gly-Leu-Phe-Asp-Thr-Ala-Gly

Rac1 Inhibitor F56, control peptide (Cat. No. 2222)

Rac1 Inhibitor W56 (Cat. No. 2221) is a 16-mer peptide comprising residues 45-60 of the GEF recognition/activation site of Rac1. The peptide selectively inhibits Rac1 interaction with TrioN, GEF-H1 and Tiam1. Rac1 Inhibitor F56, control peptide (Cat. No. 2222) has the same sequence as Rac1 Inhibitor W56, but with the tryptophan replaced with a phenylalanine residue. This peptide does not affect GEF-Rac1 interaction.

Gao *et al* (2001) Trp^{56} of Rac1 specifies interaction with a subset of guanine nucleotide exchange factors. J.Biol.Chem. ***276*** 47530.

NSC 23766



.3HCl

In vitro NSC 23766 (Cat. No. 2161) selectively inhibits Rac1 binding and activation by Rac-specific guanine nucleotide exchange factors (GEFs) TrioN and Tiam1 (IC_{50} ~ 50 μM). The compound exhibits no detectable effects on Cdc42 or RhoA activation by their respective GEFs, or Rac1 binding to BcrGAP or PAK1. NSC 23766 selectively inhibits Rac1-mediated cell functions induced by PDGF, such as membrane ruffling and lamellipodia formation. In PC-3 prostate cancer cells, the compound dose-dependently inhibits proliferation, anchorage-independent growth and cell invasion, thus reversing the tumor cell phenotype.

Gao *et al* (2004) Rational design and characterization of a Rac GTPase-specific small molecule inhibitor. Proc.Natl.Acad.Sci.USA ***101*** 7618.

G Protein Reagents continued

			Unit size
1089	8-Bromo-cGMP, sodium salt	cGMP analog	10 mg 50 mg
1774	Dynamin inhibitory peptide	Dynamin inhibitor; blocks endocytosis	1 mg
1775	Dynamin inhibitory peptide, myristoylated	Cell-permeable dynamin inhibitor	1 mg
1776	Dynamin inhibitory peptide, myristoylated (control)	Control peptide version of Cat. Nos. 1774 and 1775	1 mg
1931	G-Protein antagonist peptide	Inhibits G protein activation by GPCRs	1 mg
1192	Mastoparan	Activates G_i and G_o	1 mg
1895	Mastoparan-7	G protein activator peptide	1 mg
1896	Mastoparan X	G protein activator peptide	1 mg
1193	Melittin	Inhibits G_s and stimulates G_i activity	500 µg
1240	NF 023	Inhibitor of $G_{o/i}$ α-subunits. Also P2X purinoceptor antagonist	10 mg 50 mg
2161	NSC 23766 3HCl New	Selective inhibitor of Rac1-GEF interaction; anti-oncogenic	10 mg 50 mg
2222	Rac1 Inhibitor F56, control peptide New	Control peptide version of Rac1 Inhibitor W56 (Cat. No. 2221)	1 mg
2221	Rac1 Inhibitor W56 New	Selective inhibitor of Rac1-GEF interaction	1 mg
1400	SCH 202676 HBr	Allosteric inhibitor of ligand binding to G protein-coupled receptors	10 mg 50 mg
1884	[D-Trp^{7,9,10}]-Substance P	Inhibits M_1 ACh receptor activation of $G_{q/11}$	1 mg
1472	Suramin hexasodium salt	Uncouples G proteins from receptors. Also purinoceptor antagonist	100 mg

Ion Channel Modulators

Calcium Channel Modulators

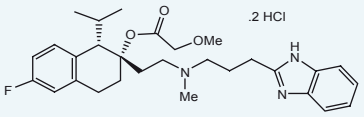
1544	(±)-Bay K 8644	Ca^{2+} channel activator (L-type)	10 mg 50 mg
1545	(*R*)-(+)-Bay K 8644	Ca^{2+} channel blocker (L-type)	10 mg 50 mg
1546	(*S*)-(-)-Bay K 8644	Ca^{2+} channel activator (L-type)	10 mg 50 mg
0685	Diltiazem HCl	Ca^{2+} channel blocker (L-type)	1 g
1403	FPL 64176	Potent activator of L-type Ca^{2+} channels	10 mg 50 mg
2004	Isradipine	Ca^{2+} channel blocker (L-type)	10 mg 50 mg
2198	Mibefradil 2HCl New	Selective T-type Ca^{2+} channel blocker	10 mg 50 mg
1075	Nifedipine	Ca^{2+} channel blocker (L-type)	100 mg
1124	(*R*)-(-)-Niguldipine HCl	Less active enantiomer of Cat. No. 1123	10 mg 50 mg
1123	(*S*)-(+)-Niguldipine HCl	Ca^{2+} channel blocker (L-type)	10 mg 50 mg
0600	Nimodipine	Ca^{2+} channel blocker (L-type)	100 mg
0601	Nitrendipine	Ca^{2+} channel blocker (L-type)	50 mg
2268	NNC 55-0396 2HCl New	Highly selective T-type Ca^{2+} channel inhibitor	10 mg
0654	Verapamil HCl	Ca^{2+} channel blocker (L-type)	1 g
0840	Loperamide HCl	Ca^{2+} channel blocker (HVA) (L/N-type)	1 g
1085	ω-Conotoxin GVIA	Ca^{2+} channel blocker (N-type)	250 µg
1084	ω-Conotoxin MVIIC	Ca^{2+} channel blocker (N, P and Q-type)	100 µg
1439	Ruthenium Red	Non-selective Ca^{2+} channel blocker (N- and P-type)	100 mg
0806	Gabapentin	Anticonvulsant. Binds to voltage-sensitive Ca^{2+} channels	10 mg 50 mg
1147	SKF 96365 HCl	Receptor-operated calcium channel blocker	10 mg 50 mg
1806	SR 33805 oxalate	Ca^{2+} channel blocker; binds allosterically to distinct site on L-type channels	10 mg

Calcium Channel Modulators continued

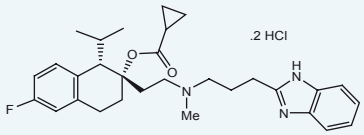
Selective T-type calcium channel antagonists, Mibefradil and NNC 55-0396

Selectivity for T-type channels

Mibefradil (Ro 40-5967; Cat. No. 2198) and its more selective structural analog NNC 55-0396 (Cat. No. 2268) are inhibitors of T-type Ca^{2+} channels. Mibefradil antagonizes both T-type and high-voltage-activated (HVA) Ca^{2+} channels, although it shows moderate selectivity for T-type channels (~ 6-fold; IC_{50} values are 2.7 and 18.6 μM for T-type and L-type channels respectively). The block of HVA channels by mibefradil can be attributed to the production of an active metabolite, des-methoxyacetyl mibefradil, which is not produced by the structurally modified compound NNC 55-0396. Thus NNC 55-0396 displays much greater selectivity towards T-type channels. The IC_{50} for inhibition of recombinant Cav3.1 T-type channels is 6.8 μM, compared to > 100 μM for antagonism of HVA currents in INS-1 cells.



Mibefradil (Cat. No. 2198)



NNC 55-0396 (Cat. No. 2268)

Activity *in vivo*

Mibefradil has a unique cardiovascular profile and displays antihypertensive effects *in vivo*. The antagonist is a potent vasodilator with high selectivity for the coronary vasculature over the peripheral vasculature and the myocardium. It is more potent in increasing coronary artery flow (EC_{50} = 54 nM) than in suppressing aortic and myocardial contractility (IC_{50} values are 275 and 14000 nM, respectively). Importantly, mibefradil relaxes vascular muscle and slows the heart rate without producing negative inotropy or reflex tachycardia.

Osterrieder and Holck (1989) In vitro pharmacologic profile of Ro 40-5967, a novel Ca^{2+} channel blocker with potent vasodilator but weak inotropic action. J.Cardiovasc. Pharmacol. ***13*** 754. **Mehrke** *et al* (1994) The Ca(++)-channel blocker Ro 40-5967 blocks differently T-type and L-type Ca++ channels. J.Pharmacol.Exp.Ther. ***271*** 1483. **Clozel** *et al* (1997) Discovery and main pharmacological properties of mibefradil (Ro 40-59670), the first selective T-type calcium blocker. J.Hypertens.Suppl. ***15*** S17. J.Cardiovasc.Pharmacol. ***18*** Suppl 10 S55. **Huang** *et al* (2004) NNC 55-0396 [(1S,2S)-2-(2-(N-[(3-benzimidazol-2-yl)propyl]-N-methylamino)ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphtyl cyclopropanecarboxylate dihydrochloride]: A new selective inhibitor of T-type calcium channels. J.Pharmacol.Exp.Ther. ***309*** 193. **Li** *et al* (2005) Towards selective antagonists of T-type calcium channels: design, characterization and potential applications of NNC 55-0396. Cardiovasc. Drug.Rev. ***23*** 173.

Chloride Channel Modulators

			Unit Size
0963	9-AC	Chloride transport inhibitor	100 mg
1412	Chromanol 293B	Blocks I_{CFTR}. Also I_{Ks} blocker	10 mg
			50 mg
1422	DCEBIO	Activates Cl^- conductance and hIK1 K^+ channels	10 mg
			50 mg
1540	DCPIB New	Selective blocker of VSAC/ICl,swell; inhibits glucose-stimulated insulin release	10 mg
			50 mg
0911	Glibenclamide	Blocks CFTR Cl^- channels. Also K_{ATP} channel blocker	100 mg
1646	Lonidamine	CFTR Cl^- channel blocker. Also anticancer agent	10 mg
			50 mg
0593	NPPB	Chloride channel blocker	50 mg

Potassium Channel Modulators

ATP-Activated

1377	Cromakalim	K_{ATP} channel opener	10 mg
			50 mg
0964	Diazoxide	K^+ channel opener (K_{ATP})	100 mg
0911	Glibenclamide	K^+ channel blocker (K_{ATP})	100 mg
2396	Glimepiride New	K^+ channel opener (K_{ATP})	10 mg
			50 mg
1378	Levcromakalim	K_{ATP} channel opener. Active enantiomer of Cromakalim (Cat. No. 1377)	10 mg
			50 mg
0583	Minoxidil	K^+ channel opener	100 mg
2147	Nicorandil	K_{ATP} channel opener and NO donor	50 mg
1355	P1075	Potent K_{ATP} channel opener	10 mg
			50 mg
1503	Pinacidil	K^+ channel opener. Activates K_{ATP} channels	50 mg
2095	PNU 37883 HCl New	Vascular K_{ATP} channel blocker	10 mg
			50 mg
2076	Y-26763	K_{ATP} channel opener	10 mg
			50 mg

ATP-Activated Potassium Channel Modulators continued

			Unit size
2077	Y-27152	Prodrug of K_{ATP} channel opener Y-26763; orally active *in vivo*	10 mg 50 mg
0882	ZM 226600	K_{ATP} channel opener	10 mg 50 mg

Ca^{2+}-Activated

1652	Apamin	K^+ channel blocker (small conductance, Ca^{2+}-dependent)	1 mg
1087	Charybdotoxin	K^+ channel blocker (high conductance, Ca^{2+}-dependent)	10 µg
1422	DCEBIO	More potent analog of 1-EBIO (Cat. No. 1041). Activates hIK1/Cl^- conductance	10 mg 50 mg
0674	Dequalinium dichloride	K^+ channel blocker (SK_{Ca})	100 mg
1041	1-EBIO	Activator of epithelial K_{Ca} channels	10 mg 50 mg
1086	Iberiotoxin	K^+ channel blocker (high conductance, Ca^{2+}-dependent)	100 µg
2006	Paxilline	Potent blocker of BK_{Ca} channels	10 mg
1310	UCL 1684	Highly potent blocker of SK_{Ca}	5 mg

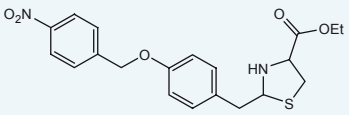
Inward Rectifiers

1316	Tertiapin-Q	Potent, selective inhibitor of inward-rectifier K^+ channels	1 mg

Voltage-Gated

0876	AM 92016 HCl	K^+ channel blocker (K_V)	10 mg 50 mg
1412	Chromanol 293B	I_{Ks} blocker. Also blocks I_{CFTR}	10 mg 50 mg
1475	(-)-[3*R*,4*S*]-Chromanol 293B	I_{Ks} blocker. Enantiomer of Cat. No. 1412	10 mg 50 mg
1399	CP 339818 HCl	Non-peptide, potent Kv1.3 channel blocker	10 mg 50 mg
1808	E-4031 2HCl New	K^+ (HERG) channel blocker; inhibits rapid delayed rectifier K^+ current (I_{Kr})	10 mg 50 mg
1999	Linopirdine 2HCl	KCNQ channel blocker	10 mg 50 mg
2000	XE 991 2HCl	Potent, selective KCNQ channel blocker; blocks M-current	10 mg 50 mg

Selective Na^+/Ca^{2+}-exchange inhibitor



SN-6 (Cat. No. 2184) is an analog of KB-R7943 (Cat. No. 1244) that is a novel and selective inhibitor of the reverse mode of the cell membrane-located Na^+/Ca^{2+}-exchanger (NCX). The inhibitor is more selective for NCX over other receptors than KB-R7943, displays a preference for NCX1, and has potential use as an anti-ischemic agent.

Selectivity for the reverse mode of NCX

SN-6 selectively inhibits NCX isoforms, with some selectivity for NCX1 (IC_{50} values are 2.9, 16 and 8.6 µM for inhibition of intracellular Na^+-dependent $^{45}Ca^{2+}$ uptake by cells expressing NCX1, NCX2 and NCX3 respectively (see table)). The inhibition appears to be of mixed competitive and non-competitive type. SN-6 preferentially inhibits the reverse mode of NCX, as it has little effect on extracellular Na^+-dependent Ca^{2+} efflux mediated by NCX1 (IC_{50} > 30 µM). In addition, the inhibitor does not significantly affect uptake into cells transfected with the K^+-dependent Na^+/Ca^{2+} exchanger NCKX2 and has minimal affinity for a range of receptors and ion channels (IC_{50} > 30 µM). SN-6 displays moderate affinity for the muscarinic ACh receptor (IC_{50} = 18 µM), however the affinity is lower than that shown by KB-R7943 (see table below).

	NCX1	NCX2	NCX3	mAChR
SN-6	2.9[1]	16.0[1]	18.6[1]	18[1]
KB-R7943	4.3[2]	4.7[2]	1.4[2]	0.71[1]

IC_{50} values for inhibition of $^{45}Ca^{2+}$ uptake in CCL39 fibroblasts transfected with NCX isoforms and for inhibition of [^{3}H]-QNB binding to the mACh receptor. Data taken from 1. Iwamoto *et al* (2004) and 2. Iwamoto *et al* (2001).

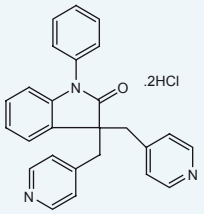
Anti-ischemic effects

NCX1 is highly expressed in the heart, kidney and brain. In a hypoxia/reoxygenation injury model (porcine renal proximal tubule cells over-expressing NCX1) SN-6 potently and dose-dependently protects against cell damage (IC_{50} = 0.63 µM). SN-6 has also been reported to protect against ischaemia/referfusion injury in perfused guinea pig Langendorff hearts.

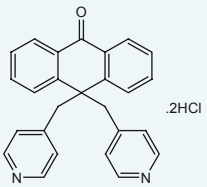
Iwamoto *et al* (2004) The exchanger inhibitory peptide region-dependent inhibition of Na^+/Ca^{2+} exchange by SN-6 [2-[4-(4-nitrobenzyloxy)benzyl]thiazolidine-4-carboxylic acid ethyl ester], a novel benzyloxyphenyl derivative. Mol.Pharmacol. ***66*** 45. **Iwamoto** (2004) Forefront of Na^+/Ca^{2+} exchanger studies: molecular pharmacology of Na^+/Ca^{2+} exchange inhibitors. J.Pharmacol.Sci. ***96*** 27.

Voltage-Gated Potassium Channel Modulators continued

XE 991 and Linopirdine, M-current blockers



Linopirdine dihydrochloride (Cat. No. 1999)



XE 991 dihydrochloride (Cat. No. 2000)

The M-current is a slowly activating and deactivating potassium conductance that is essential for regulating neuronal electrical excitability and responsiveness to synaptic inputs. It is widely believed that the M-current is mediated via heteromeric KCNQ2 and KCNQ3 subunit-forming voltage-gated potassium channels. XE 991 (Cat. No. 2000) and linopirdine (DuP 996) (Cat. No. 1999) are orally-active cognition enhancers that selectively block KCNQ channels, including the M-current and homomeric KCNQ1 channels.

Potent blockade of M-currents
XE 991 and linopirdine block native M-currents in sympathetic neurons with IC_{50} values of 0.98 and 3.4-7 μM respectively. The blockers also inhibit currents through cloned heteromeric KCNQ2/3 channels with similar potencies (see table below for values).

Selective for KCNQ over other voltage-gated K^+ channels
In addition to their activity at KCNQ2/3 channels, XE 991 and linopirdine block homomeric KCNQ1 channels (IC_{50} values are 0.75 and 8.9 μM respectively). XE 991 shows selectivity over the KCNQ1/minK complex (K_d = 11.1 μM), a channel involved in the pathogenesis of long QT syndrome, and displays > 40-fold selectivity over other voltage-gated potassium channels.

Enhancement of neurotransmitter release and cognition *in vitro* and *in vivo*
In vitro, XE 991 and linopirdine increase [^{3}H]ACh release from rat hippocampal slices (EC_{50} values are 0.49 and 4.2 μM respectively). Following oral administration in rats *in vivo*, XE 991 and linopirdine increase neurotransmitter release and enhance cognition.

The selectivity and potency of XE 991 at KCNQ channels, and the oral activity of both XE 991 and linopirdine should make them essential tools for studying M-currents *in vitro* and *in vivo*.

Schnee and Brown (1998) Selectivity of linopirdine (DuP 966), a neurotransmitter release enhancer, in blocking voltage-dependent and calcium-activated potassium currents in hippocampal neurons. J.Pharmacol.Exp.Ther. ***286*** 709. **Wang** *et al* (1998) KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. Science ***282*** 1890. **Zaczek** *et al* (1998) Two new potent neurotransmitter release enhancers, 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracenone and 10,10-bis(2-fluoro-4-pyridinylmethyl)-9(10H)-anthracenone: comparison to linopirdine. J.Pharmacol.Exp.Ther. ***285*** 724. **Wang** *et al* (2000) Molecular basis for differential sensitivity of KCNQ and I_{Ks} channels to the cognitive enhancer XE991. Mol.Pharmacol. ***57*** 1218. **Passmore** *et al* (2003) KCNQ/M currents in sensory neurons: significance for pain therapy. J.Neurosci. ***23*** 7227.

	M-current	KCNQ2 +3	KCNQ2	KCNQ1	KCNQ1 +minK1	eag1	erg1	erg3	elk1	Kv1.2	Kv4.3
XE 991	0.98	0.6	0.71	0.75	11.1 (K_d)	49	> 100	> 100	> 100	> 100	43
Linopirdine	7.0	4.0	4.8	8.9	-	31	53	85	37	68	86

IC_{50} values (in μM) for blockade of M-current and cloned potassium channels by XE 991 and linopirdine. Data taken from Wang *et al* (1998).

Other

			Unit Size
0940	4-Aminopyridine	K^+ channel blocker	100 mg
2330	DMP 543 New	K^+ channel blocker and potent ACh release enhancer	10 mg
			50 mg
0385	SG 209	K^+ channel opener	10 mg
			50 mg
0416	YS-035 HCl	Inhibits K^+ outward/pacemaker current	10 mg
			50 mg

Sodium Channel Modulators

2404	Ambroxol HCl New	Na^+ channel blocker	50 mg
0890	Amiloride HCl	Na^+ channel blocker	100 mg
1470	Flecainide acetate	Cardiac Na^+ channel blocker. Antiarrhythmic	10 mg
			50 mg
0522	Flunarizine 2HCl	Dual Na^+/Ca^{2+} channel (T-type) blocker	500 mg
1539	β-Pompilidotoxin	Slows neuronal Na^+ channel inactivation	1 mg
1043	QX 222	Na^+ channel blocker	10 mg
			50 mg
1014	QX 314 bromide	Na^+ channel blocker	100 mg
0768	Riluzole HCl	Na^+ channel blocker	25 mg
			100 mg
1078	Tetrodotoxin	Na^+ channel blocker	1 mg
1069	Tetrodotoxin citrate	Citrate salt of Cat. No. 1078	1 mg
0757	Vinpocetine	Na^+ channel blocker	50 mg

Ion Transport Modulators

			Unit size
1234	A23187, free acid	Calcium ionophore	10 mg
1334	Bafilomycin A1	H^+-ATPase (vacuolar) inhibitor	10 µg
1236	BHQ	Inhibitor of SERCA ATPase	100 mg
1114	CGP 37157	Antagonist of motochondrial Na^+/Ca^{2+} exchange	10 mg
			50 mg
1235	Cyclopiazonic Acid	Inhibitor of SERCA ATPase	10 mg
			50 mg
0507	Dantrolene, sodium salt	Ca^{2+} release inhibitor	100 mg
0839	DHBP dibromide	Ca^{2+} release inhibitor	100 mg
1704	Ionomycin calcium salt	Calcium ionophore	1 mg
2092	Ionomycin free acid	Calcium ionophore	1 mg
1244	KB-R7943 mesylate	Na^+/Ca^{2+} exchange inhibitor (reverse mode)	10 mg
			50 mg
1866	MRS 1845	Potent SOC inhibitor; capacitative Ca^{2+} entry	10 mg
			50 mg
1291	Ochratoxin A	Stimulates SERCA-ATP-dependent Ca^{2+} pump activity	1 mg
1076	Ouabain	Na^+,K^+-ATPase inhibitor	100 mg
2006	Paxilline	SERCA ATPase blocker. Also potent BK_{Ca} channel blocker	10 mg
1439	Ruthenium Red	Inhibits ryanodine-sensitive Ca^{2+} release and mitochondrial uptake/release	100 mg
1329	Ryanodine	Ca^{2+} release inhibitor	5 mg
1147	SKF 96365 HCl	Inhibits receptor-mediated Ca^{2+} entry	10 mg
			50 mg
2184	SN-6 New	Selective Na^+/Ca^{2+} exchange inhibitor (reverse mode)	10 mg
			50 mg
1138	Thapsigargin	Potent inhibitor of SERCA ATPase	1 mg

Other Ion Channel Modulators

2090	CALP1	Inhibits Ca^{2+}-sensitive ion channels; acts from cytoplasmic side	1 mg
1950	Gap 26	Gap junction blocker; inhibits smooth muscle contraction and IP_3-mediated ATP release	1 mg
1476	Gap 27	Selective gap junction blocker	1 mg
1611	Lamotrigine	Blocks Na^+, K^+ and Ca^{2+} channels; inhibits glutamate release	10 mg
			50 mg
2289	Lamotrigine isethionate New	Water-soluble form of Cat. No. 1611	10 mg
			50 mg
1724	Tocriscreen Ion Channel Modulators	Collection of ion channel modulators	1 set
2202	Zatebradine HCl New	Bradycardic agent; blocks I_f pacemaker current	10 mg
			50 mg
1000	ZD 7288	Sino-atrial node function modulator (I_f inhibitor)	10 mg
			50 mg

Lipid Signaling Agents

Cyclooxygenase Inhibitors

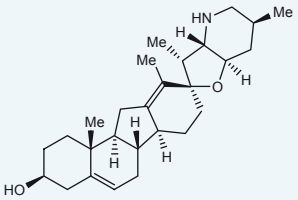
1706	Acetaminophen	Cyclooxygenase inhibitor; may be selective for COX-3	100 mg
1430	DuP 697	Cyclooxygenase (COX-2) inhibitor	10 mg
			50 mg
1769	Flurbiprofen	Cyclooxygenase inhibitor	100 mg
1507	FR 122047 HCl	Cyclooxygenase (COX-1) inhibitor	10 mg
			50 mg
1708	Indomethacin	Cyclooxygenase inhibitor (COX-1 > COX-2)	100 mg
0960	Piroxicam	Cyclooxygenase (COX-1) inhibitor	100 mg
1418	Resveratrol	Cyclooxygenase inhibitor	100 mg
1707	Sulindac	Cyclooxygenase inhibitor (following metabolism to sulindac sulfide)	100 mg

Hedgehog Signaling Reagents

			Unit size
1639	AY 9944 2HCl	Inhibitor of hedgehog (hh) signaling. Inhibits Δ^7-dehydrocholesterol reductase	10 mg
1623	Cyclopamine	Inhibitor of hedgehog (hh) signaling	1 mg
1974	SANT-1 New	Inhibitor of hedgehog (hh) signaling; antagonizes smoothened activity	10 mg 50 mg
1638	U 18666A	Inhibitor of hedgehog (hh) signaling. Also inhibits cholesterol synthesis	10 mg

Cyclopamine – hedgehog signaling inhibitor

Cyclopamine (Cat. No. 1623) is an inhibitor of hedgehog (hh) signaling, which acts via direct inhibition of smoothened, the accessory protein to the putative hh receptor patched. It displays anti-cancer and teratogenic properties *in vivo*.



Incardona *et al* (2000) Cyclopamine inhibition of sonic hedgehog signal transduction is not mediated through effects on cholesterol transport. Dev.Biol. ***224*** 440. **Chen** *et al* (2002) Inhibition of hedgehog signaling by direct binding of cyclopamine to smoothened. Genes Dev. ***16*** 2743. **King** (2002) Roughing up smoothened: chemical inhibitors of hedgehog signaling. J.Biol. ***1*** 8. **Scott** (2003) Cancer: a twist in a hedgehog's tale. Nature ***425*** 780.

Inositol Lipid Reagents

Properties of PI 3-Kinase Inhibitors

PI 3-Kinase Inhibitor	Cat. No.	Action	IC_{50}
LY 294002	1130	Selective	1.4 μM[1]
Quercetin	1125	Non-selective	3.8 μM[2]
Wortmannin	1232	Selective, irreversible, cell-permeable	2-4 nM[3]

1. **Vlahos** *et al* (1994) J.Biol.Chem. ***269*** 5241. 2. **Matter** *et al* (1992) Biochem.Biophys.Res.Comm. ***186*** 624. 3. **Powis** *et al* (1994) Cancer Res. ***54*** 2419.

1224	2-APB	Membrane permeable IP_3 receptor antagonist	10 mg 50 mg
1420	D-*myo*-Inositol-1,3,4,5-*tetrakis*phosphate, octapotassium salt	Potent inhibitor of Ins(1,4,5)P_3 5-phosphatase. Metabolite of Cat. No. 1482	100 μg
1482	D-*myo*-Inositol-1,4,5-trisphosphate, hexapotassium salt	Ca^{2+} mobilizing second messenger	1 mg
0681	L-690,330	Inositol monophosphatase inhibitor	10 mg 50 mg
0682	L-690,488	Cell-permeable prodrug of the IMPase inhibitor L-690,330 (Cat. No. 0681)	5 mg
1130	LY 294002 HCl	Selective PI 3-kinase inhibitor	5 mg 25 mg
1042	*N*-Methyllidocaine iodide	Enhances biosynthesis of phosphatidylinositol	10 mg 50 mg
2368	Anti-PIP2 New	Antibody recognizing PIP2	100 μg
1125	Quercetin	Non-selective PI 3-kinase inhibitor	100 mg
1232	Wortmannin	Potent, irreversible inhibitor of PI 3-kinase	1 mg 5 mg
1983	740 Y-P New	Cell-permeable PI 3-kinase activator	1 mg

Lipoxygenase Inhibitors

1761	Baicalein	5- and 12-Lipoxygenase inhibitor	50 mg
1304	BW-B 70C	5-Lipoxygenase inhibitor	10 mg 50 mg
2204	STEARDA New	Endogenous inhibitor of 5-lipoxygenase	10 mg
0645	2-(1-Thienyl)ethyl 3,4-dihydroxybenzylidenecyanoacetate	5-, 12-, 15-Lipoxygenase inhibitor	10 mg 50 mg

Phospholipase Inhibitors

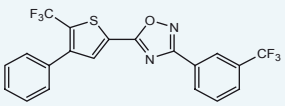
			Unit size
1462	AACOCF$_3$	Phospholipase A$_2$ inhibitor	5 mg
			25 mg
1437	D609	Selective PC-PLC inhibitor	10 mg
			50 mg
1941	*m*-3M3FBS	Phospholipase C activator	10 mg
1942	*o*-3M3FBS	Inactive analog of *m*-3M3FBS (Cat. No. 1941)	10 mg
0606	OBAA	Phospholipase A$_2$ inhibitor	10 mg
			50 mg
1460	PACOCF$_3$	Phospholipase A$_2$ inhibitor	10 mg
1268	U 73122	Phospholipase C inhibitor	10 mg
			50 mg

General Lipid Signaling Agents

0355	(±)-Acetylcarnitine chloride	Intermediate in lipid metabolism	100 mg
0477	(±)-Decanoylcarnitine chloride	Intermediate in lipid metabolism	50 mg
0526	(±)-Hexanoylcarnitine chloride	Intermediate in lipid metabolism	50 mg
2392	JTE 013 New	S1P$_2$ receptor antagonist	10 mg
0548	(±)-Lauroylcarnitine chloride	Intermediate in lipid metabolism	50 mg
1311	MK 886	Inhibitor of 5-lipoxygenase-activating protein (FLAP)	10 mg
			50 mg
0567	(±)-Myristoylcarnitine chloride	Intermediate in lipid metabolism	50 mg
0605	(±)-Octanoylcarnitine chloride	Intermediate in lipid metabolism	50 mg
0878	Oleamide	Sleep-inducing brain lipid	10 mg
			50 mg
1484	Oleylethanolamide	Lipid mediator, anorexic actions	10 mg
			50 mg
0611	(±)-Propionylcarnitine chloride	Intermediate in lipid metabolism	50 mg
2194	R 59-022 New	Diacylglycerol kinase inhibitor; increases PKC activity	10 mg
			50 mg
2284	SEW 2871 New	Cell-permeable, selective S1P$_1$ receptor agonist	10 mg
			50 mg
2097	SKI II New	Selective non-lipid inhibitor of sphingosine kinase; antitumor	10 mg
			50 mg
1370	Sphingosine-1-phosphate	Bioactive lipid, binds EDG receptors	1 mg
1736	Tocriscreen Lipid Signaling	Collection of lipid signaling tools	1 set

Selective S1P$_1$ receptor agonist – SEW 2871

SEW 2871 (Cat. No. 2284) is a novel, potent sphingosine-1-phosphate 1 (S1P$_1$) receptor agonist. The highly selective compound activates human S1P$_1$ receptors with an EC$_{50}$ of 13 nM, but does not activate S1P$_2$, S1P$_3$, S1P$_4$ or S1P$_5$ receptors at concentrations up to 10 μM. SEW 2871 is cell-permeable and active *in vivo*.



Hale *et al* (2004) A rational utilization of high-throughput screening affords selective, orally bioavailable 1-benzyl-3-carboxyazetidine sphingosine-1-phosphate-1 receptor agonists. J.Med.Chem. ***47*** 6662. **Sanna** *et al* (1994) Sphingosine 1-phosphate (S1P) receptor subtypes S1P$_1$ and S1P$_3$, respectively, regulate lymphocyte recirculation and heart rate. J.Biol.Chem. ***279*** 13839. **Bolick** *et al* (2005) Sphingosine-1-phosphate prevents tumor necrosis factor-α-mediated monocyte adhesion to aortic endothelium in mice. Arterioscler.Thromb.Vasc.Biol. ***25*** 976.

Nitric Oxide Tools

NO Synthase Inhibitors

Properties of Selected NO Synthase Inhibitors

Inhibitor	iNOS	nNOS	eNOS
Aminoguanidine (0787)	31	170	330
7-Nitroindazole (0602)	9.7	8.3	11.8
L-NIL (1139)	1.6	37	49
L-NMMA (0771)	6.6	4.9	3.5
L-NNA (0664)	3.1	0.29	0.35
1400W (1415)	0.23	7.3	1000

The IC$_{50}$ values (in μM) shown are for inhibition of the human NOS isoforms under identical conditions. For full experimental conditions, please refer to the cited publication.
Alderton *et al* (2001) Nitric oxide synthases: structure, function and inhibition. Biochem.J. ***357*** 593.

nNOS (Neuronal/Type I/NOS-1/bNOS)

			Unit size
0735	3-Bromo-7-nitroindazole	Selective nNOS inhibitor	10 mg
			50 mg
1200	N^{ω}-Propyl-L-arginine	Highly selective inhibitor of nNOS	10 mg
			50 mg

iNOS (Inducible/Type II/NOS-2)

0787	Aminoguanidine HCl	Irreversible iNOS inhibitor	100 mg
0871	AMT HCl	Potent, selective iNOS inhibitor	10 mg
			50 mg
0673	L-Canavanine sulfate	iNOS inhibitor	25 mg
0873	EIT HBr	Selective iNOS inhibitor, acts arginine binding site	10 mg
			50 mg
0951	2-Iminopiperidine HCl	Selective iNOS inhibitor	10 mg
			50 mg
0897	*S*-Isopropylisothiourea HBr	iNOS inhibitor, acts arginine binding site	10 mg
			50 mg
0776	*S*-Methylisothiourea sulfate	Highly selective iNOS inhibitor	10 mg
			50 mg
1139	L-NIL HCl	Selective iNOS inhibitor	10 mg
			50 mg
1415	1400W 2HCl	Potent, highly selective iNOS inhibitor	10 mg
			50 mg

eNOS (Endothelial/Type III/NOS-3)

0546	L-NIO 2HCl	Potent eNOS inhibitor	10 mg
			50 mg

Non-Selective NOS Inhibitors

0665	L-NAME HCl	Non-selective NOS inhibitor	100 mg
0800	7-NINA	Sodium salt of Cat. No. 0602	10 mg
			50 mg
0602	7-Nitroindazole	Non-selective NOS inhibitor	50 mg
0771	L-NMMA acetate	Non-selective NOS inhibitor	10 mg
			50 mg
0664	L-NNA	NOS inhibitor (nNOS = eNOS >> iNOS)	100 mg
0919	TRIM	nNOS/iNOS inhibitor	50 mg

NO Donors/Precursors

0722	*N*-Acetyl-*N*-acetoxy-4-chlorobenzenesulfonamide	Nitroxyl precursor	10 mg
			50 mg
0663	L-Arginine	Endogenous substrate for NOS	100 mg
2147	Nicorandil	NO donor and K_{ATP} channel opener	50 mg
0756	SIN-1 chloride	Water-soluble NO donor	50 mg
0598	SNAP	A stable analog of endogenous *S*-nitroso compounds	10 mg
			50 mg
0603	SNOG	NO carrier. Breaks down to release NO	10 mg
			50 mg
1135	Spermine NONOate	Slow NO releasing agent	10 mg
			50 mg

Indirect Modulators of NO Activity

0772	Carboxy-PTIO, potassium salt	Stable, water-soluble deactivator of NO	10 mg
			50 mg
0476	2,4-Diamino-6-hydroxypyrimidine	Inhibits biosynthesis of tetrahydrobiopterin and thus NOS	50 mg
0504	Diphenyleneiodonium chloride	Binds to flavoproteins and inhibits NOS	10 mg
			50 mg
0880	ODQ	Selective inhibitor of NO-sensitive guanylyl cyclase	10 mg
			50 mg
0727	Pyrrolidinedithiocarbamate ammonium	Inhibits NF-κB, prevents increase in NOS mRNA	50 mg

Other Nitric Oxide Reagents

1726	Tocriscreen Nitric Oxide	Collection of nitric oxide tools	1 set

Antibodies for Cancer Research

NEW! High quality, primary mouse monoclonal antibodies for the study of cancer and signal transduction mechanisms.

Product	Clone	Subclass	Species Reactivity	Applications	Cat.No.	Unit Size
Anti-Cdk1 and Cdk2 (human)	AN21.2	IgG2a	Human, mouse, *Xenopus*	IB, ELISA	2356	100 µg
Anti-Cdk2 (human)	AN4.3	IgG2a	Human, mouse, *Xenopus*	IB, ELISA	2357	100 µg
Anti-EGFR (human)	EGFR1	IgG2b	Human, horse	IB, IP, IHC	2361	100 µg
Anti-EGFR (human)	F4	IgG1	Human. Not yet tested in other species	IB, IP, IHC, ELISA	2362	100 µg
Anti-c-erbB3 (human)	RTJ2	IgG1	Human. Not yet tested in other species	IB, IP, IHC, ELISA	2380	100 µg
Anti-c-erbB4 (human)	HFR1	IgG2b	Human, mouse. Not yet tested in other species	IB, IP, IHC	2379	100 µg
Anti-FGF-3 (human)	MSD1	IgG2a	Human, mouse, *Xenopus*	IB, IHC	2363	100 µg
Anti-c-Jun (human)	C-J 4c4/1	IgG1	Human, rat. Not yet tested in other species	IB, ELISA	2358	100 µg
Anti-MDM2 (human)	SMP 14	IgG1	Human, rat, mouse	IB, IP, IHC, ELISA	2377	100 µg
Anti-phospho-MDM2 (Ser^{186}) (human)	2G2	IgG1	Human. Not yet tested in other species	IB	2381	100 µg
Anti-N-Myc (human)	NMYC-1	IgG2a	Human, mouse	IB, IP	2360	100 µg
Anti-NCAM (human)	ERIC-1	IgG1	Human. Not yet tested in other species	IB, IP, IHC, ELISA	2364	100 µg
Anti-$p14^{ARF}$ (human)	ARF 4C6/4	IgG2a	Human. Not yet tested in other species	IB, IP, ELISA	2366	100 µg
Anti-p53 (human)	PAb240	IgG1 kappa	Human, mouse, rat, hamster, chicken, bovine, monkey	IB, IP, IHC, ELISA	2369	100 µg
Anti-p53 (human)	PAb 1802	IgG1	Human, mouse. Not yet tested in other species	IB, IP, IHC, ELISA	2375	100 µg
Anti-p53 (human)	DO-2	IgG2a	Human. Not yet tested in other species	IB, IP, IHC	2376	100 µg
Anti-p53 (human)	PAb 1801	IgG1	Human. Not yet tested in other species	IB, IP, IHC, ELISA	2378	100 µg
Anti-PIP2 (human)	PIP2 2C11	IgM	Human. Not yet tested in other species	IB, IP, ELISA	2368	100 µg
Anti-PKC (human)	MC5	IgG2a	Human, rat, mouse	IB, IP, ELISA	2367	100 µg
Anti-VEGF (human)	VG-1	IgG1	Human. Not yet tested in other species	IB, IP, IHC, ELISA	2355	100 µg

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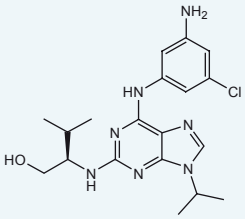
www.tocris.com

Protein Kinase Reagents

Cyclin-Dependent Kinase Inhibitors

Selective cdk inhibitor – Aminopurvalanol A



Aminopurvalanol A (Cat. No. 2072) is a cell-permeable, selective cyclin-dependent kinase (cdk) inhibitor. It causes cell cycle arrest in the G_2-phase, and induces cellular differentiation and apoptosis.

Selective over other kinases

Aminopurvalanol A is a potent inhibitor of cdk1/cyclin B, cdk2/cyclin A, cdk2/cyclin E, and cdk5/p35 (see table on page 18). It is over 3000-fold selective over a range of other protein kinases (IC_{50} > 100 μM) and is at least 90-fold selective over ERK1, ERK2, CK-1 and InsRTK.

Causes differentiation, cell cycle arrest and apoptosis

In studies using *Xenopus* egg extracts and human U937 leukemic cells, aminopurvalanol A binds and inactivates cdk1 and cdk2, resulting in G_2-phase cell cycle arrest (IC_{50} = 1.25 μM). It also causes differentiation and at high concentrations (> 10 μM) triggers apoptotic cell death.

Inhibits cdk1 activity

Although aminopurvalanol A potently inhibits both cdk1 and cdk2, it is reported that the compound preferentially inhibits the activity of cdk1. The inhibitory effect on G_2/M cell-cycle progression suggests that the primary functional target of aminopurvalanol A is cdk1/cyclin B.

The selectivity of this inhibitor should make it a useful tool to elucidate the role of cdks in cell cycle regulation.

Chang *et al* (1999) Synthesis and application of functionally diverse 2,6,9-trisubsistuted purine libraries as CDK inhibitors. Chem.Biol. ***6*** 361. **Rosiana** *et al* (1999) A cyclin-dependent kinase inhibitor inducing cancer cell differentiation: biochemical identification using *Xenopus* egg extracts. Proc.Natl.Acad.Sci.USA ***96*** 4797. **Knockaert** *et al* (2000) Intracellular targets of cyclin-dependent kinase inhibitors: identification by affinity chromatography using immobilised inhibitors. Chem.Biol. ***7*** 411.

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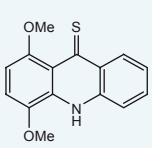
			Unit size
2072	Aminopurvalanol A	Cyclin-dependent kinase inhibitor	10 mg
			50 mg
2356	Anti-Cdk1 and Cdk2 New	Antibody recognizing Cdk1 and Cdk2	100 μg
2357	Anti-Cdk2 New	Antibody recognizing Cdk2	100 μg
1813	Indirubin-3´-oxime	Cyclin-dependent kinase inhibitor. Also inhibits other protein kinases	10 mg
			50 mg
1398	Kenpaullone	Potent cyclin-dependent kinase inhibitor. Also inhibits GSK-3	10 mg
2152	NSC 625987 New	Cyclin-dependent kinase 4 (cdk4) inhibitor	10 mg
			50 mg
1867	NSC 663284 New	Cdc25 phosphatase inhibitor; blocks cdk1 and cdk2 activation	10 mg
1937	NSC 693868	Cdk inhibitor. Also inhibits GSK-3	10 mg
			50 mg
1284	Olomoucine	Cyclin-dependent kinase inhibitor	5 mg
			25 mg
1902	[Ala[92]]-p16 (84-103)	Cyclin-dependent kinase inhibitor	1 mg
1580	Purvalanol A	Cyclin-dependent kinase inhibitor	10 mg
			50 mg
1581	Purvalanol B	Cyclin-dependent kinase inhibitor	10 mg
			50 mg

NSC 625987, a selective cdk4 inhibitor



NSC 625987 (Cat. No. 2152) is a cyclin-dependent kinase (cdk) 4 inhibitor (IC_{50} = 0.2 μM at cdk4/cyclin D1). It displays > 500-fold selectivity over cdk2 (IC_{50} > 100 μM for cdc2/cyclin A, cdk2/cyclin A and cdk2/cyclin E).

Kubo *et al* (1999) The p16 status of tumor cell lines identifies small molecule inhibitors specific for cyclin-dependent kinase 4. Clin.Cancer Res. ***5*** 4279. **McInnes** *et al* (2004) Structural determinants of CDK4 inhibition and design of selective ATP competitive inhibitors. Chem.Biol. ***11*** 525.

Cyclin-Dependent Kinase Inhibitors continued

Properties of Cdk Inhibitors

Kinase	Aminopurvalanol A[1] Cat. No. 2072	Purvalanol A[2] Cat. No. 1580	Purvalanol B[2] Cat. No. 1581	Olomoucine[3] Cat. No. 1284
cdc2/cyclin B	–	4	6	7
cdk1/cyclin B	0.033	–	–	–
cdk2/cyclin A	0.033	70	6	7
cdk2/cyclin E	0.028	35	9	7
cdk4/cyclin D	–	850	> 10000	> 1000
cdk5/p35	0.020	75	6	3
cdk6/cyclin D3	–	–	–	> 250
ERK1	12.0	9000	3333	50
ERK2	3.1	–	–	40
PKC	> 100	> 10000	> 10000	> 800
PKA	18.0	9000	3800	> 2000
PKG	> 100	> 10000	> 100000	> 2000
InsRTK	4.4	5000	2200	400
MLCK	–	–	–	> 1000

Data is given as IC_{50} values (μM). For full experimental details and assay conditions used, please refer to the cited publications.

ERK1 and 2 = externally regulated kinases PKC = protein kinase C PKA = protein kinase A PKG = protein kinase G InsRTK = insulin receptor tyrosine kinase MLCK = myosin light chain kinase

1. **Chang** *et al* (1999) Chem.Biol. ***6*** 361. 2. **Gray** *et al* (1998) Science ***281*** 533. 3. **Vesely** *et al* (1994) Eur.J.Biochem. ***224*** 771.

Glycogen Synthase Kinase Reagents

L803 – a novel inhibitor of GSK-3

L803 (Cat. No. 2235) is a novel phosphorylated peptide, derived from the recognition motif of GSK-3, which acts as a GSK-3β inhibitor (IC_{50} = 150 μM). In contrast to other inhibitors that are ATP-competitive, L803 competes for the substrate binding site of GSK-3. At 200 μM, the compound displays minimal inhibition of a range of other protein kinases including Cdc2, MAPK, PKA, CK2, PKCδ or PKB.

Lys-Glu-Ala-Pro-Pro-Ala-Pro-Pro-Gln-pSer-Pro

Plotkin *et al* (2003) Insulin mimetic action of synthetic phosphorylated peptide inhibitors of glycogen synthase kinase-3. J.Pharmacol.Exp.Ther. ***305*** 974.

			Unit size
1802	2B-(SP)	Selective GSK-3 phosphopeptide substrate	1 mg
1835	FRATide	GSK-3 inhibitor	500 μg
1813	Indirubin-3´-oxime	GSK-3β inhibitor. Also inhibits other protein kinases	10 mg
			50 mg
1398	Kenpaullone	GSK-3 inhibitor. Also inhibits cdks	10 mg
2235	L803 New	Substrate-competitive inhibitor of GSK-3	1 mg
1937	NSC 693868	GSK-3 inhibitor. Also inhibits cdks	10 mg
			50 mg
1352	Phospho-Glycogen Synthase Peptide-2 (substrate)	GSK-3 substrate (synthetic)	500 μg
1616	SB 216763	Potent, selective GSK-3 inhibitor	10 mg
			50 mg
1617	SB 415286	Potent, selective GSK-3 inhibitor	10 mg
			50 mg
2236	TCS 183 New	Fragment 1-13 of GSK-3β sequence	1 mg
2320	TCS 184 New	Scrambled control peptide for use with TCS 183	1 mg

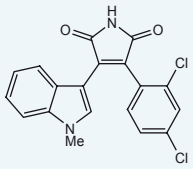
Glycogen Synthase Kinase Reagents continued

Properties of Selected GSK-3 Inhibitors

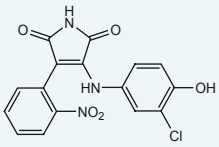
Inhibitor	Cat. No.	Action	IC_{50} (μM)
Indirubin-3´-oxime	1813	Non-selective	0.19[1]
NSC 693868	1937	Non-selective	1[2]
SB 216763	1616	Potent, selective	0.009[3]
SB 415286	1617	Potent, selective	0.031[3]

1. **Bain** *et al* (2003) Biochem.J. ***371*** 199. 2. **Ortega** *et al* (2002) Bioorg.Med.Chem.Lett. ***10*** 2177. 3. **Coghlan** *et al* (2000) Chem.Biol. ***7*** 793.

Potent and selective inhibitors of GSK-3



SB 216763 (Cat. No. 1616)



SB 415286 (Cat. No. 1617)

Glycogen synthase kinase (GSK) is regulated by many extracellular stimuli, including growth factors, insulin and cell adhesion. The kinase's activity has been suggested to play a pivotal role in the regulation of numerous signaling pathways elicited by these external stimuli. SB 216763 (Cat. No. 1616) and SB 415286 (Cat. No. 1617) are novel, cell-permeable and selective inhibitors of this enzyme.

Selective for GSK-3
SB 216763 and SB 415286 potently inhibit GSK-3α *in vitro* (K_i values are 9 and 31 nM respectively) in a manner that is competitive with respect to ATP. These compounds do not significantly inhibit 24 other protein kinases, including PKA, PKC, MAPK, SAPK, AMPK and CK-II (IC_{50} > 10 μM).

Inhibit cellular GSK-3 activity and provide neuroprotection
SB 216763 and SB 415286 activate glycogen synthase (through direct inhibition of GSK-3) in cells *in vitro*. The inhibitors stimulate glycogen synthesis in human liver cells and stimulate the expression of a β-catenin-regulated reporter gene in HEK-293 cells. SB 216763 and SB 415286 also display neuroprotective properties in primary neurons *in vitro*, a result of inhibiting protein kinase B signaling via GSK-3.

The availability of these novel, potent, selective and cell-permeable inhibitors of GSK-3 should help identify the roles of this important enzyme in cell signaling and survival.

Coghlan *et al* (2000) Selective small molecule inhibitors of glycogen synthase kinase-3 modulate glycogen metabolism and gene transcription. Chem.Biol. ***7*** 793. **Cross** *et al* (2001) Selective small-molecule inhibitors of glycogen synthase kinase-3 activity protect primary neurones from death. J.Neurochem. ***77*** 94. **Culbert** *et al* (2001) GSK-3 inhibition by adenoviral FRAT1 overexpression is neuroprotective and induces Tau dephosphorylation and β-catenin stabilisation without elevation of glycogen synthase activity. FEBS Lett. ***507*** 288.

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MAP Kinase Reagents

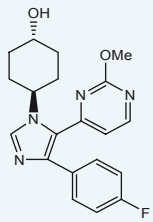
Properties of MAP Kinase Inhibitors

Inhibitor	Cat. No.	Action	IC_{50} Value
PD 98059	1213	MEK inhibitor	2-7 μM[1]
SB 202190	1264	Potent p38 MAP kinase inhibitor	50 nM (SAPK2a/p38)[2] 100 nM (SAPK2b/p38β2)[2]
SB 203580	1202, 1402	p38 MAP kinase inhibitor	50 nM (SAPK2a/p38)[2] 500 nM (SAPK2b/p38β2)[2]
SB 239063	1962	Potent, selective p38 MAP kinase inhibitor; orally active	44 nM (p38α)[3]
SL 327	1969	Selective inhibitor of MEK1 and MEK2; brain penetrant	0.18 μM (MEK1)[4] 0.22 μM (MEK2)[4]
SP 600125	1496	Selective JNK inhibitor	40 nM (JNK1 and 2)[5] 90 nM (JNK3)[5]
U0126	1144	MEK1 and MEK2 inhibitor	72 nM (MEK1)[6] 58 nM (MEK2)[6]

1. **Alessi** *et al* (1995) J.Biol.Chem. ***270*** 27489. 2. **Davies** *et al* (2000) Biochem.J. ***351*** 95. 3. **Underwood** *et al* (2000) J.Pharmacol.Exp.Ther. ***293*** 281. 4. **Scherle** *et al* (2000) J.Biol.Chem. ***275*** 37086. 5. **Bennett** *et al* (2001) Proc.Natl.Acad.Sci.USA ***98*** 13681. 6. **Favata** *et al* (1998) J.Biol.Chem. ***273*** 18623.

MAP Kinase Reagents continued

Orally active, potent p38 inhibitor, SB 239063



SB 239063 (Cat. No. 1962) is a novel, potent and selective second-generation p38 MAP kinase inhibitor (IC_{50} = 44 nM for inhibition of recombinant purified human p38α). It displays > 200-fold selectivity over ERK, JNK1 and other kinases, and shows improved selectivity, cellular and *in vivo* activity over first-generation inhibitors such as SB 203580 (Cat. Nos. 1202 and 1402).

Anti-inflammatory activity

SB 239063 has anti-inflammatory activity and potently reduces inflammatory cytokine production. It inhibits eosinophil recruitment and enhances apoptosis of eosinophils cultured from guinea pig airways.

Neuroprotective *in vitro* and *in vivo*

In vitro, SB 239063 protects primary neurons from mild to moderate excitotoxic injury. *In vivo*, SB 239063 is neuroprotective when administered orally before moderate ischemic stroke. Additionally, poststroke i.v. administration in rats reduces infarct volume and neurological deficits in both moderate and severe permanent stroke models.

Underwood *et al* (2000) SB 239063, a potent p38 MAP kinase inhibitor, reduces inflammatory cytokine production, airways eosinophil infiltration, and persistence. J.Pharmacol.Exp.Ther. ***293*** 281. **Barone** *et al* (2001) SB 239063, a second-generation p38 mitogen-activated protein kinase inhibitor, reduces brain injury and neurological deficits in cerebral focal ischemia. J.Pharmacol.Exp.Ther. ***296*** 312. **Legos** *et al* (2002) The selective p38 inhibitor SB-239063 protects primary neurons from mild to moderate excitotoxic injury. Eur.J.Pharmacol. ***447*** 37.

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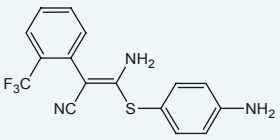
			Unit size
1290	Anisomycin	Activates JNK/SAPK/p38 MAP kinase	10 mg 50 mg
1777	Arctigenin	Potent MKK1 inhibitor. Also inhibits IκBα phosphorylation	10 mg 50 mg
2186	CMPD-1 New	Non-ATP-competitive p38α inhibitor	10 mg 50 mg
2363	Anti-FGF-3 Y New	Antibody recognizing FGF-3	100 µg
1565	JIP-1 (153-163)	JNK-selective inhibitor peptide	1 mg
2358	Anti-c-Jun Y New	Antibody recognizing c-Jun	100 µg
1989	c-JUN peptide	Peptide inhibitor of JNK/c-Jun interaction	1 mg
1878	MAPK Cascade Inhibitor Tocriset	Selection of 5 MAPK cascade inhibitors (Cat. Nos. 1110, 1213, 1321, 1144 and 1202)	1 set
1879	MAPK Inhibitor Tocriset	Selection of 5 MAPK inhibitors (Cat. Nos. 1213, 1202, 1264, 1496 and 1144)	1 set
2243	MEK Inhibitor Tocriset New	Selection of 3 MEK inhibitors (Cat. Nos. 1213, 1969 and 1144)	1 set
2244	p38 MAPK Inhibitor Tocriset New	Selection of 3 p38 MAPK inhibitors (Cat. Nos. 1264, 1202 and 1962)	1 set
1213	PD 98059	Specific inhibitor of MEK	10 mg 50 mg
1264	SB 202190	Potent, selective inhibitor of p38 MAPK	10 mg 50 mg
1202	SB 203580	Selective inhibitor of p38 MAPK	10 mg 50 mg
1402	SB 203580 hydrochloride	Selective inhibitor of p38 MAPK; water-soluble	10 mg
1962	SB 239063	Potent, selective p38 MAP kinase inhibitor; orally active	10 mg
2008	SKF 86002 2HCl New	p38 MAP kinase inhibitor; anti-inflammatory agent	10 mg 50 mg
1969	SL 327	Selective inhibitor of MEK1 and MEK2; brain penetrant	10 mg
1496	SP 600125	Novel and selective JNK inhibitor	10 mg 50 mg
1868	U0124	Inactive analog of U0126 (Cat. No. 1144)	10 mg
1144	U0126	Potent, selective inhibitor of MEK1 and 2	5 mg 25 mg

MAP Kinase Reagents continued

SL 327 – a brain penetrant inhibitor of MEK1 and 2

SL 327 (Cat. No. 1969) is a selective inhibitor of MEK1 and 2 (IC_{50} values are 0.18 and 0.22 μM for MEK1 and MEK2 respectively). Upon systemic administration *in vivo*, SL 327 blocks ERK activation but not JNK or p38 phosphorylation.



In vitro – effects on LTP

Inhibition of the MAPK/ERK cascade by SL 327 prevents CREB and Elk-1 phosphorylation, resulting in a rapidly decaying hippocampal long-term potentiation (LTP).

Brain penetrant *in vivo*

Systemic administration of SL 327 in mice inhibits ERK phosphorylation. The inhibitor acts as a neuroprotectant following ischemic brain injury, reducing infarct size and improving neurological function. SL 327 (50-100 mg/kg, i.p.) also blocks fear conditioning and learning in rats.

Atkins *et al* (1998) The MAPK cascade is required for mammalian associative learning. Nature Neurosci. ***1*** 602. **Davis** *et al* (2000) The MAPK/ERK cascade targets both Elk-1 and cAMP response element-binding protein to control long-term potentiation-dependent gene expression in the dentate gyrus *in vivo*. J.Neurosci. ***20*** 4563. **Scherle** *et al* (2000) Regulation of cyclooxygenase-2 induction in the mouse uterus during decidualization. An event of early pregnancy. J.Biol.Chem. ***275*** 37086. **Wang** *et al* (2003) Significant neuroprotection against ischemic brain injury by inhibition of the MEK1 protein kinase in mice: exploration of potential mechanism associated with apoptosis. J.Pharmacol.Exp.Ther. ***304*** 172.

	MEK1	MEK2	ERK1	MKK3/p38	MKK4	JNK	PKC
SL 327	0.18	0.22	> 50	21	> 100	> 100	> 10

IC_{50} values (in μM) for inhibition of various protein kinases. Data taken from Scherle *et al* (2000).

PI 3-Kinase Reagents

			Unit size
1130	LY 294002 HCl	Selective PI 3-kinase inhibitor	5 mg
			25 mg
1125	Quercetin	Non-selective PI 3-kinase inhibitor	100 mg
1232	Wortmannin	Potent, irreversible inhibitor of PI 3-kinase	1 mg
			5 mg
1983	740 Y-P New	Cell-permeable PI 3-kinase activator	1 mg

740 Y-P – a cell-permeable activator of PI 3-kinase

740 Y-P (Cat. No. 1983) is a phosphopeptide that binds with high affinity to the p85 subunit of PI 3-kinase and activates the enzyme *in vitro*. The peptide is derived from the p85 binding site on the activated PDGF receptor, coupled to an internalisation vector to allow cell-permeability.

Arg-Gln-Ile-Lys-Ile-Trp-Phe-Gln-Asn-Arg-Arg-Met-Lys-Trp-Lys-Lys-Ser-Asp-Gly-Gly-pTrp-Met-Asp-Met-Ser

PI 3-kinase-dependent mitogenic activity

740 Y-P is an agonist for cell growth and produces a mitogenic response in cultured C2 muscle cells. The peptide stimulates entry into S-phase more effectively than EGF and FGF. The ability of 740 Y-P to stimulate cell proliferation is inhibited by wortmannin, LY 294002 and rapamycin, suggesting the effect is mediated via activation of the PI 3-kinase/p70 S6 kinase cascade. The peptide response is not inhibited by the MEK inhibitor PD 98059 (Cat. No. 1213) and does not stimulate ERK phosphorylation.

Promotes neuronal cell survival

In serum-free cultures, 740 Y-P rescues rat cerebellar granule neurons from cell death. The peptide survival response is dependent on PI 3-kinase activity, but not p70 S6 kinase activity.

Derossi *et al* (1998) Stimulation of mitogenesis by a cell-permeable PI 3-kinase binding peptide. Biochem.Biophys.Res.Comm. ***251*** 148. **Williams and Doherty** (1999) Evidence for and against a pivotal role of PI 3-kinase in a neuronal cell survival pathway. Mol.Cell.Neurosci. ***13*** 272.

Other Ser/Thr Kinase Reagents

Inhibition of Protein Kinases by Broad Spectrum Inhibitors

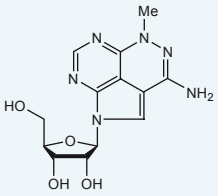
Inhibitor	Cat. No.	PKA	PKG	CaMK	MLCK	PKC	CK-I	CK-II	References
A-3	0366	4.3	3.8	–	7	47	80	5.1	1
Chelerythrine	1330	170	–	> 100	–	0.7	–	–	2 (IC_{50})
GF 109203X	0741	33	4.6	–	0.6	0.032	–	–	3 (IC_{50})
H-7	0542	3	5.8	–	97	6	100	780	1
H-9	0396	1.9	0.9	60	70	18	110	> 300	1
KT 5720	1288	0.06	> 2	–	–	> 2	–	–	4
ML-9	0431	32	–	–	4	54	–	–	1
Staurosporine	1285	0.008	0.009	0.02	0.0013	0.005	–	–	5,6,7

Data is given as K_i values (μM) unless otherwise stated. For full experimental details and assay conditions used, please refer to the cited publications.

PKA= protein kinase A PKG = protein kinase G CaMK = Ca^{2+}/calmodulin kinase II MLCK = myosin light chain kinase CK-I and CK-II = casein kinase I and II

1. **Hidaka and Koybashi** (1992) Ann.Rev.Pharmacol.Toxicol. ***32*** 377. 2. **Herbert** *et al* (1990) Biochem.Biophys.Res.Comm. ***172*** 993. 3. **Jacobson** *et al* (1995) J.Pharmacol. Exp.Ther. ***275*** 995. 4. **Kase** *et al* (1987) Biochem.Biophys.Res.Comm. ***142*** 436. 5. **Meijer** (1996) TiCB ***6*** 393. 6. **Yanagihara** *et al* (1991) J.Neurochem. ***56*** 294. 7. **Bucholz** *et al* (1991) Hypertension ***17*** 91.

Selective Akt Pathway Inhibitor – API-2



API-2 (triciribine) (Cat. No. 2151) is a selective inhibitor of Akt (protein kinase B) signaling, which displays minimal inhibition of PKC, PKA, SGK and p38 pathways. The compound does not inhibit upstream regulators of Akt such as PI-3 kinase and PDK1. Instead, API-2 is suggested to act via inhibition of phosphorylation and activation of downstream targets of Akt including Bad, GSK-3β and AFX. *In vitro*, the inhibitor induces apoptosis and growth arrest preferentially in human cancer cells with aberrant Akt expression/activity. In a tumor xenograft mouse model, API-2 potently and selectively inhibits the growth of human tumors that overexpress Akt. The compound also inhibits DNA synthesis and displays antiviral against HIV-1 and -2.

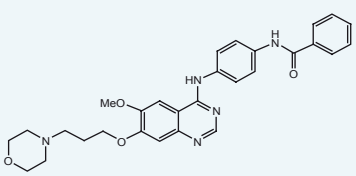
Wotring *et al* (1990) Dual mechanisms of inhibition of DNA synthesis by triciribine. Cancer Res. ***50*** 4891. **Ptak** *et al* (1998) Phosphorylation of triciribine is necessary for activity against HIV type 1. AIDS Res.Hum.Retroviruses. ***14*** 1315. **Yang** *et al* (2004) Akt/protein kinase B signaling inhibitor-2, a selective small molecule inhibitor of Akt signaling with antitumour activity in cancer cells overexpressing Akt. Cancer Res. ***64*** 4394.

			Unit size
0366	A-3 HCl	Protein kinase inhibitor	10 mg
2422	AKTide-2T New	Akt/PKB substrate (synthetic)	1 mg
1353	Akt/SKG Substrate Peptide	Akt/PKB substrate (synthetic)	1 mg
2151	API-2 New	Selective inhibitor of Akt/PKB signaling. Antitumor and antiviral	10 mg
1227	Apigenin	Protein kinase inhibitor	10 mg
			50 mg
1688	Autocamtide-2-related inhibitory peptide	Selective CaM kinase II inhibitor	1 mg
0543	C-1	Protein kinase C inhibitor	10 mg
			50 mg
2442	CGP 53353 New	Selective inhibitor of PKCβII	10 mg
1330	Chelerythrine chloride	Potent protein kinase C inhibitor	5 mg
1458	DAPK Substrate Peptide	Death associated protein kinase substrate (synthetic)	1 mg
0749	Dihydrosphingosine	Protein kinase C inhibitor	10 mg
			50 mg
0484	Dioctanoylglycol	Diacylglycerol kinase inhibitor	50 mg
2088	DMNB	DNA-dependent protein kinase inhibitor	10 mg
			50 mg
0541	Fasudil HCl	Inhibitor of cyclic nucleotide dependent- and Rho-kinases	10 mg
			50 mg
0741	GF 109203X	Protein kinase C inhibitor	10 mg
1883	cGMP Dependent Kinase Inhibitor Peptide	Inhibitor of protein kinases G and A	1 mg
1381	GW 5074	Potent, selective cRaf1 kinase inhibitor	10 mg
			50 mg
0542	H-7 2HCl	Protein kinase inhibitor	10 mg
			50 mg
0396	H-9 2HCl	Protein kinase inhibitor	10 mg
			50 mg
1813	Indirubin-3′-oxime	Protein kinase inhibitor	10 mg
			50 mg

Other Ser/Thr Kinase Reagents continued

			Unit size
1683	K 252a	Protein kinase inhibitor	200 µg
1277	KN-62	CaM kinase II inhibitor	1 mg
1278	KN-93	CaM kinase II inhibitor	1 mg
1288	KT 5720	Selective protein kinase A inhibitor	100 µg
1289	KT 5823	Selective protein kinase G inhibitor	100 µg
1878	MAPK Cascade Inhibitor Tocriset	Selection of 5 MAPK cascade inhibitors (Cat. Nos. 1110, 1213, 1321, 1144 and 1202)	1 set
1900	[Ala^{107}]-MBP (104-118)	Protein kinase C inhibitor	1 mg
1901	[Ala^{113}]-MBP (104-118)	Protein kinase C inhibitor	1 mg
1193	Melittin	Inhibits protein kinase C and cAMP-dependent protein kinase	500 µg
1880	Mixed Kinase Inhibitor Tocriset	Selection of 5 mixed kinase inhibitors (Cat. Nos. 0741, 1277, 1288, 1289 and 1285)	1 set
0431	ML 9 HCl	Myosin light chain kinase inhibitor	10 mg 50 mg
1926	MLCK inhibitor peptide	Myosin light chain kinase inhibitor	1 mg
1885	MLCK inhibitor peptide 18	Selective inhibitor of myosin light chain kinase	1 mg
1628	NPC 15437 2HCl	Selective protein kinase C inhibitor	10 mg 50 mg
0609	(±)-Palmitoylcarnitine chloride	Protein kinase C inhibitor	50 mg
1201	Phorbol 12-myristate 13-acetate	Protein kinase C activator	1 mg 5 mg
1904	PKA inhibitor fragment (6-22) amide	Potent protein kinase A inhibitor	1 mg
1882	PKA Tocriset	Selection of 5 PKA modulators (Cat. Nos. 1337, 1140, 1099, 1288 and 1603)	1 set
2367	Anti-PKC ϒ New	Antibody recognizing PKC	100 µg
1887	PKC fragment (530-558)	Potent activator of protein kinase C	1 mg
1792	PKC β pseudosubstrate	Selective cell-permeable PKC inhibitor peptide (attached to vector)	1 mg
1791	PKC ζ pseudosubstrate	PKC ζ inhibitor peptide (attached to cell-permeable vector)	1 mg
1790	Pseudo RACK1	Protein kinase C activator peptide (attached to cell-permeable vector)	1 mg
2194	R 59-022 New	Diacylglycerol kinase inhibitor; increases PKC activity	10 mg 50 mg
2002	Ro 31-8220 mesylate New	Protein kinase inhibitor	10 mg
1610	Rottlerin	Reported PKCδ inhibitor	10 mg 50 mg
1614	SB 431542	Potent, selective inhibitor of TGF-β receptor ALK5, ALK4 and 7	10 mg
0433	SC-9	Protein kinase C activator	10 mg 50 mg
0430	SC-10	Protein kinase C activator	10 mg 50 mg
0633	D-*erythro*-Sphingosine (synthetic)	Protein kinase C inhibitor	10 mg 50 mg
1285	Staurosporine	Non-selective protein kinase inhibitor	100 µg
1551	STO-609 acetate	Selective CaM kinase kinase inhibitor	10 mg 50 mg
2275	TBB New	Selective cell-permeable CK2 inhibitor	10 mg 50 mg
1254	Y-27632 2HCl	Selective p160ROCK inhibitor	10 mg 50 mg
1321	ZM 336372	Potent, selective c-Raf inhibitor	10 mg 50 mg
2458	ZM 447439 New	Inhibits Aurora kinases A and B	10 mg

Novel Aurora kinase inhibitor – ZM 447439



Aurora protein kinases (A, B and C) are key regulators of mitotic events and are frequently overexpressed in cells of various cancers. ZM 447439 (Cat. No. 2458) is a novel ATP-competitive inhibitor of Aurora A and B kinases *in vitro* (IC_{50} values are 110 and 130 nM, respectively). The compound is selective over a range of other kinases including Cdk1 and PLK1 (IC_{50} > 10 µM). ZM 447439 inhibits cell division and displays selective toxicity towards proliferating tumor cells versus non-dividing cells.

Ditchfield *et al* (2003) Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2, and Cenp-E to kinetochores. J.Cell Bio. ***161*** 267. **Gadea and Ruderman** (2005) Aurora kinase inhibitor ZM447439 blocks chromosome-induced spindle assembly, the completion of chromosome condensation, and the establishment of the spindle integrity checkpoint in *Xenopus* egg extracts. Mol.Biol. Cell ***16*** 1305. **Jung** *et al* (2006) Discovery of novel and potent thiazoloquinazolines as selective Aurora A and B kinase inhibitors. J.Med.Chem. ***49*** 955.

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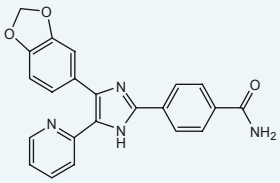
Other Ser/Thr Kinase Reagents continued

SB 431542 – a potent, selective inhibitor of ALK5



TGF-β is a cytokine involved in biological processes such as cell differentiation, growth, migration, adhesion and survival. Receptors for this cytokine include the type I and type II receptors, of which activin receptor-like kinase 5 (ALK5) is the type I receptor. SB 431542 (Cat. No. 1614) is an inhibitor selective for ALK5 and the closely related proteins ALK4 (activin type I receptor) and ALK7 (nodal type I receptor).

Selective *in vitro*

SB 431542 inhibits the phosphorylation of Smad3 (the substrate of ALK5) with an IC_{50} value of 94 nM. SB 431542 also inhibits the phosphorylation of Smad2 by ALK5, 4 and 7. The inhibitor has no significant activity at a range of other protein kinases, including AMPK, JNK1, PKA, p38 MAPK, casein kinase 2, ALK2 and ALK6 (IC_{50} ≥ 10 μM).

Inhibits TGF-β signaling

The compound inhibits TGF-β-induced nuclear Smad3 localization and TGF-β-induced production of fibronectin mRNA and the extracellular matrix component collagen *in vitro*.

This inhibitor of the TGF-β receptor ALK5, and its relatives ALK4 and ALK7, should help to elucidate the roles of TGF-β, activin and nodal signaling.

Laping *et al* (2002) Inhibition of transforming growth factor (TGF)-β1-induced extracellular matrix with a novel inhibitor of the TGF-β type I receptor kinase activity: SB-431542. Mol.Pharmacol. ***62*** 58. **Inman** *et al* (2002) SB-431542 is a potent and specific inhibitor of transforming growth factor-β superfamily type I activin receptor-like kinase (ALK) receptors ALK4, ALK5, and ALK7. Mol.Pharmacol. ***62*** 65.

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Inhibition of Protein Kinases by Y-27632 (Cat. No. 1254)

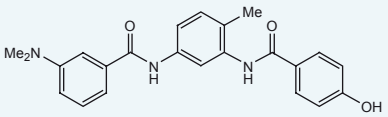
	p160ROCK	PKA	PKC	MLCK	ROCK II	PRK2	MSK1	MAPKAP-K1b	PHK
Y-27632	0.14[1]	25[1]	26[1]	> 250[1]	0.8 (IC_{50})[2]	0.6 (IC_{50})[2]	8.3 (IC_{50})[2]	19 (IC_{50})[2]	44 (IC_{50})[2]

K_i values (μM) unless otherwise stated

MAPKAP-K1b = mitogen-activated protein kinase-activated protein kinase-1b MLCK = myosin light chain kinase MSK1 = mitogen- and stress-activated protein kinase-1 PHK = phosphorylase kinase PKA = cAMP-dependent protein kinase PKC = protein kinase C PRK2 = protein kinase C-related protein kinase 2 p160ROCK = Rho-associated protein kinase ROCK II = Rho-dependent protein kinase (isoenzyme of p160ROCK)

1. **Uehata** *et al* (1997) Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase. Nature ***389*** 990. 2. **Davies** *et al* (2000) Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochem.J. ***351*** 95.

Potent, selective inhibitor of c-Raf – ZM 336372



ZM 336372 (Cat. No. 1321) is a potent and selective inhibitor of Raf isoforms *in vitro*. ZM 336372 inhibits human c-Raf with an IC_{50} of 70 nM, is 10-fold selective over B-Raf. The inhibitor is also 30-fold selective over SAPK2/p38 and is selective over 17 other protein kinases (up to 50 μM), including: PKA, PKBα, PKC, p70 S6 kinase, p42 MAPK and CDK1. Paradoxically, incubation of cells with ZM 336372 induces > 100-fold activation of c-Raf, without triggering any activation of MKK1 or p42 MAPK/ERK2, and this is thought to be due to activation of a novel feedback loop whereby Raf suppresses its own activation.

- **IC_{50} = 70 nM for c-Raf**
- **10-fold selective over B-Raf**
- **Selective over many other protein kinases (up to 50 μM)**

ZM 336372 is an important tool that may provide insight into mechanisms involved in the Ras/MAP kinase cascade.

Hall-Jackson *et al* (1999) Paradoxical activation of Raf by a novel Raf inhibitor. Chem.Biol. ***6*** 559. **Wartenberg** *et al* (2001) Down-regulation of intrinsic p-glycoprotein expression in multicellular prostate tumor spheroids by reactive oxygen species. J.Biol.Chem. ***276*** 17420.

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	c-Raf	B-Raf	SAPK2a	SAPK2b	PKA	PKC	MAPKAP-K1b,2 and 3	CK2	p42MAPK	MEK1 and 4	SAPK1/JNK	SAPK3 and 4	Cyclin B/Cdk1
ZM 336372	0.07	~ 0.8	2	2	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50

IC_{50} values (μM). Data taken from Hall-Jackson *et al* (1999).

Cdk1 = cyclin-dependent protein kinase-1 CK2 = casein kinase-2 JNK = c-jun N-terminal kinase MAPK = mitogen-activated protein kinase MAPKAP-K1b, 2 and 3 = mitogen-activated protein kinase-activated protein kinases 1b, 2 and 3 MEK = MAPK kinase PHK = phosphorylase kinase PKA = cAMP-dependent protein kinase PKC = protein kinase C SAPK = stress-activated protein kinase

Protein Tyrosine Kinase Reagents

Inhibition of Protein Tyrosine Kinases by the Tyrphostins

Inhibitor	Alternative Name(s)	Cat. No.	EGFR	Her2-Neu	PDGFR	Trk	InsR	Comments
AG 18	Tyrphostin A23/ RG-50810	0493	35[a]	–	25[c]	> 100	4000[a], 1200[a] (K_i)	Broad spectrum[1,2,3,4]
AG 99	–	0497	10[a]	–	–	–	410[a] (K_i)	Selective for EGFR over InsR[3,5]
AG 213	Tyrphostin AG 213	0503	2.4[a]	–	3[c]	> 100	640[a] (K_i)	Potent, broad spectrum. Also inhibits PKC (IC_{50} = 60 μM)[1,3,4]
AG 825	Tyrphostin AG 825	1555	19[b]	0.15[b]	40[b]	–	> 100[b]	Selective for Her2 over Her1[8,9]
AG 1478	Tyrphostin AG 1478	1276	0.003	> 100	> 100	–	–	Highly selective for EGFR[4]
AG 490	Tyrphostin AG 490	0414	2[a]	13.5[b]	–	–	–	Selective for EGFR over Her2Neu. Also inhibits Jak2, Jak3[6,7]
Tyrphostin B44	–	0578	0.4[a]	37[b]	–	–	–	More active enantiomer[6]
Tyrphostin B44, (+) enantiomer	–	0579	0.86[a]	–	–	–	–	Less active enantiomer[6]
AG 555	Tyrphostin AG 555	0618	0.7[a]	35[b]	–	–	> 100	Selective for EGFR over Her2Neu[4]
AG 494	–	0619	0.7[a]	42[b]	6	–	> 100	Selective for EGFR over Her2Neu[4,6]
AG 556	Tyrphostin AG 556	0616	1.1[a]	> 500[b]	–	–	–	Selective for EGFR over InsR kinase[6]

Data is given as IC_{50} values (μM) unless otherwise indicated. For full experimental details and assay conditions used, please refer to the cited publications.

[a]PolyGAT / Poly GT phosphorylation assay
[b]*In vitro* autophosphorylation assay
[c]*In vitro* phosphorylation of intracellular substrates

EGFR = epidermal growth factor receptor
PDGFR = platelet-derived growth factor receptor
InsR = insulin receptor

1. **Levitski and Gilon** (1991) TiPS ***12*** 171. 2. **Ohmichi** (1993) Biochemistry ***32*** 4650. 3. **Gazit** *et al* (1989) J.Med.Chem. ***32*** 2344. 4. **Levitski and Gazit** (1995) Science ***267*** 1782. 5. **Gazit** *et al* (1996) J.Med.Chem. ***39*** 4905. 6. **Gazit** *et al* (1991) J.Med.Chem. ***34*** 189. 7. **Wang** *et al* (1999) J.Immunol. ***162*** 3897. 8. **Gazit** *et al* (1993) J.Med.Chem. ***36*** 3556. 9. **Osherov** *et al* (1993) J.Biol.Chem. ***268*** 11134.

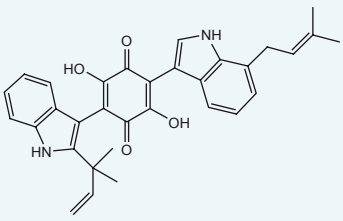
Reviews: **Lawrence and Niu** (1998) Protein kinase inhibitors: the tyrosine-specific protein kinases. Pharmacol.Ther. ***77*** 81. **Zwick** *et al* (1999) The EGF receptor as central transducer of heterologous signalling systems. TiPS ***20*** 408.

			Unit size
1930	*N*-Acetyl-*O*-phosphono-Tyr-Glu Dipentylamide	Phosphopeptide ligand for src SH2 domain	1 mg
1927	*N*-Acetyl-*O*-phosphono-Tyr-Glu-Glu-Ile-Glu	Phosphopeptide ligand for src SH2 domain	1 mg
0493	AG 18	EGFR/PDGFR-kinase inhibitor	10 mg 50 mg
0497	AG 99	EGFR-kinase inhibitor	10 mg 50 mg
0503	AG 213	EGFR/PDGFR-kinase inhibitor	10 mg 50 mg
0414	AG 490	EGFR-kinase inhibitor. Also Jak2, Jak3 inhibitor	10 mg 50 mg
0619	AG 494	Potent EGFR-kinase inhibitor	10 mg 50 mg
0618	AG 555	Potent EGFR-kinase inhibitor	10 mg 50 mg
0616	AG 556	EGFR-kinase inhibitor	10 mg 50 mg
1555	AG 825	EGFR-kinase inhibitor, selective for Her2	10 mg 50 mg
1276	AG 1478 HCl	Highly potent EGFR-kinase inhibitor	10 mg 50 mg
2417	BIBU 1361 New	Selective inhibitor of EGFR-kinase	10 mg
2416	BIBX 1382 New	Highly selective EGFR-kinase inhibitor	10 mg
1935	Caffeic acid-pYEEIE	Phosphopeptide ligand for src SH2 domain	1 mg
1819	Demethylasterriquinone B1	Selective insulin RTK activator	5 mg
1222	DMPQ 2HCl	Potent inhibitor of β-type PDGFRTK	10 mg 50 mg
2361	Anti-EGFR Y New	Antibody recognizing EGFR	100 μg
2362	Anti-EGFR Y New	Antibody recognizing EGFR	100 μg

Protein Tyrosine Kinase Reagents continued

			Unit size
2380	Anti-c-erbB3 New	Antibody recognizing c-erbB3	100 µg
2379	Anti-c-erbB4 New	Antibody recognizing c-erbB4	100 µg
1110	Genistein	EGFR-kinase, topoisomerase kinase inhibitor	10 mg
			50 mg
2238	GW 441756 New	Potent, selective TrkA inhibitor	10 mg
			50 mg
2239	GW 583340 2HCl New	Potent dual EGFR/ErbB-2 inhibitor; orally active	10 mg
			50 mg
2291	1,2,3,4,5,6-Hexabromocyclohexane New	Inhibits Jak2 autophosphorylation	50 mg
1683	K 252a	Non-selective receptor tyrosine kinase inhibitor	200 µg
1331	Lavendustin A	EGFR, $p60^{c\text{-}src}$ inhibitor	1 mg
1300	LFM-A13	Potent, selective BTK inhibitor	10 mg
			50 mg
2265	Lyn peptide inhibitor New	Inhibits Lyn activation via haematopoietin βc receptor; cell-permeable	1 mg
1878	MAPK Cascade Inhibitor Tocriset	Selection of 5 MAPK cascade inhibitors (Cat. Nos. 1110, 1213, 1321, 1144 and 1202)	1 set
0577	Methyl 2,5-dihydroxycinnamate	EGFR-kinase inhibitor	10 mg
			50 mg
1037	PD 153035 HCl	EGFR-kinase inhibitor	10 mg
			50 mg
1554	Piceatannol	Tyrosine kinase inhibitor	10 mg
1397	PP 1	Potent, selective Src inhibitor	10 mg
1407	PP 2	Potent, selective Src inhibitor	10 mg
1923	pp60 c-src (521-533) (phosphorylated)	Inhibits tyrosine kinase activity of $pp60^{c\text{-}src}$ and $pp60^{v\text{-}src}$	1 mg
1155	RR-src	Tyrosine kinase substrate peptide	1 mg
1459	SU 4312	Potent inhibitor of VEGFR tyrosine kinase	10 mg
1405	(-)-Terreic acid	Selective inhibitor of BTK	10 mg
0578	Tyrphostin B44	EGFR-kinase inhibitor	10 mg
			50 mg
0579	Tyrphostin B44, (+) enantiomer	EGFR-kinase inhibitor	10 mg
			50 mg
2355	Anti-VEGF New	Antibody recognizing VEGF	100 µg
1367	ZM 39923 HCl	Potent, selective Jak3 inhibitor	10 mg
			50 mg
1366	ZM 449829	Potent, selective Jak3 inhibitor	10 mg
			50 mg

Orally-active insulin mimetic without vascular proliferative effects



Demethylasterriquinone B1 (also known as L-783,281) (Cat. No. 1819) is a fungal metabolite that is a selective activator for the insulin receptor (IR). The activator reduces glucose uptake, *in vitro* and *in vivo*, without inducing vascular proliferation, by selectively activating the PI 3-kinase/Akt signaling pathway.

Selective for IR

Demethylasterriquinone B1 activates insulin receptor tyrosine kinase (IRTK) with an EC_{50} of 3-6 µM, with maximal effect being achieved at a concentration of 10-20 µM. In contrast, insulin-like growth factor receptor I and epidermal growth factor receptors are only activated at high concentrations (EC_{50} = 100 µM).

Insulin-mimetic metabolic, but not proliferative, properties *in vitro* and *in vivo*

In addition to stimulating glucose uptake, insulin induces vascular smooth muscle cell proliferation. Demethylasterriquinone B1 does not produce this effect. In CHO cells expressing IR, demethylasterriquinone B1 induces tyrosine phosphorylation of the IR β subunit and insulin receptor substrate 1 (IRS-1). Subsequent activation of downstream PI 3-kinase and Akt phosphorylation is induced by demethylasterriquinone B1, whereas extracellular-regulated kinase (ERK), a kinase involved in proliferation (and activated by insulin), is not stimulated. Therefore, demethylasterriquinone B1 appears to be a more selective activator of the PI 3-kinase/Akt pathway than insulin.

In rat primary adipocytes and isolated soleus muscle from lean mice, demethylasterriquinone B1 potently stimulates glucose uptake (263% and 237% of basal level at 10 and 2 µM respectively). Oral administration of demethylasterriquinone B1 also dose-dependently reduces elevated blood glucose levels in diabetic db/db and ob/ob mice.

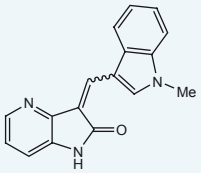
The selectivity profile of this insulin receptor activator is likely to make it a highly useful tool for studying insulin signaling pathways *in vitro* and *in vivo*.

Weber *et al* (2000) A novel insulin mimetic without a proliferative effect on vascular smooth muscle cells. J.Vasc.Surg. ***32*** 1118. **Saliturо** *et al* (2001) Discovery of a small molecule insulin receptor activator. Recent Prog.Horm.Res. ***56*** 107. **Webster** *et al* (2003) Signaling effects of demethylasterriquinone B1, a selective insulin receptor modulator. Chembiochem ***4*** 379.

Protein Tyrosine Kinase Reagents continued

NEW! Tyrosine Kinase Inhibitors

GW 441756, a potent and selective TrkA inhibitor



Tyrosine kinase receptor A (TrkA) is a member of the neurotrophin receptor family, and nerve growth factor (NGF) is its primary ligand. TrkA and NGF are overexpressed in pancreatic cancer and may play a role in a variety of other cancers.

Selective *in vitro*

GW 441756 (Cat. No. 2238) is a new inhibitor of TrkA and is more selective and potent than other established agents such as the tyrphostins, staurosporine and its analogs. GW 441756 potently inhibits TrkA (IC_{50} = 2 nM in an enzyme assay), and displays > 100-fold lower potency against a variety of other kinases including cRaf1, Cdk1 and 2, Src and VEGFR1. It is likely that the inhibitor produces its effect via the ATP-binding site.

Wood *et al* (2004) Discovery and in vitro evaluation of potent TrkA kinase inhibitors: oxindole and aza-oxindoles. Bioorg.Med.Chem.Lett. ***14*** 953.

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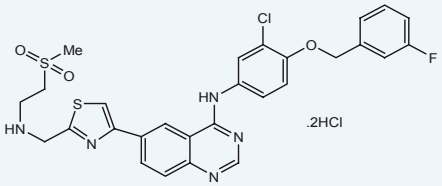
Potent, dual EGFR/ErbB-2 inhibitor – GW 583340



GW 583340 (Cat. No. 2239) is an analog of the anticancer drug GW 572016 (Lapatinib). It is an orally active dual EGFR/ErbB-2 tyrosine kinase inhibitor.

In vitro

GW 583340 potently inhibits both EGFR and ErbB-2 receptors *in vitro* (IC_{50} values are 0.01 and 0.014 μM respectively). The inhibitor attenuates growth of human tumor cells overexpressing EGFR (HN5 cells) and ErbB-2 (N87 and BT474 cells) with an average IC_{50} of 0.11 μM. This action is selective for tumor cells as GW 583340 is much less effective at inhibiting the growth of non-tumor (HFF) cells (IC_{50} > 30 μM).

Orally active anticancer agent *in vivo*

GW 583340 also has antitumor activity *in vivo*. In a human xenograft model in mice, using HN5 and BT474 cells, GW 583340 potently inhibits tumor growth: cell proliferation is inhibited by ~ 80% after 21 days (100 mg/kg per day, p.o).

Gaul *et al* (2003) Discovery and biological evaluation of potent dual ErbB-2/EGFR tyrosine kinase inhibitors: 6-thiazolylquinazolines. Bioorg.Med.Chem.Lett. ***13*** 637.

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Inhibition of Protein Tyrosine Kinases by ZM 39923 (Cat. No. 1367) and ZM 449829 (Cat. No. 1366)

Protein Kinase	ZM 39923 (pIC_{50})	ZM 449829 (pIC_{50})
Jak 3	7.1	6.8
Jak 1	4.4	4.7
EGFR	5.6	5.0
CDK4	< 5.0	< 5.0
Lck	< 5.0	< 5.0

Brown *et al* (2000) Naphthyl ketones: a new class of janus kinase 3 inhibitors. Bioorg.Med.Chem.Lett. ***10*** 575.

Other Protein Kinase Reagents

Unit size

1737 Tocriscreen Protein Kinase/
Phosphatase Tools ..... Collection of protein kinase/protein phosphatase tools ..... 1 set

Protein Phosphatase Reagents

Inhibition of Protein Phosphatases by Selected Inhibitors

Inhibitor	PP1	PP2A	PP2B	PP2C
Calyculin A (1336)	0.3-0.7	0.2-1.0	> 10,000,000	NI
Cyclosporin A (1101)	–	–	5	–
Okadaic Acid (1136)	3	0.2-1.0	> 10,000,000	NI

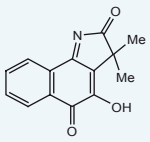
IC_{50} values in nM. NI = No inhibition

McCluskey *et al* (2002) Serine-threonine protein phosphatase inhibitors: development of therapeutic strategies. J.Med.Chem. ***45*** 1151.

			Unit size
0125	DL-AP3	Phosphoserine phosphatase inhibitor	100 mg
2176	BVT 948 New	Non-competitive protein tyrosine phosphatase inhibitor; enhances insulin signaling	10 mg
			50 mg
1891	Calcineurin Autoinhibitory Peptide	Selective calcineurin inhibitor	1 mg
1336	Calyculin A	Protein phosphatase 1 and 2A inhibitor	100 µg
1548	Cantharidin	Protein phosphatase 1 and 2A inhibitor	50 mg
0744	Ceramide	Ser/Thr protein phosphatase activator	10 mg
			50 mg
1101	Cyclosporin A	Calcineurin inhibitor	100 mg
0872	Cypermethrin	Calcineurin inhibitor (protein phosphatase 2B)	10 mg
			50 mg
1840	Fostriecin sodium salt New	Potent PP2A and PP4 inhibitor	50 µg
2162	INCA-6 New	Inhibitor of calcineurin-substrate association	10 mg
			50 mg
1547	NSC 95397	Selective Cdc25 dual specificity phosphatase inhibitor	10 mg
			50 mg
1867	NSC 663284 New	Potent, selective Cdc25 phosphatase inhibitor	10 mg
1136	Okadaic acid	Protein phosphatase 1 and 2A inhibitor	25 µg
2305	Tautomycetin New	Selective PP1 inhibitor	50 µg
1737	Tocriscreen Protein Kinase/ Phosphatase Tools	Collection of protein kinase/protein phosphatase tools	1 set

BVT 948 – a cell-permeable PTP inhibitor

BVT 948 (Cat. No. 2176) is a non-competitive, cell-permeable inhibitor of protein tyrosine phosphatases (PTPs) (IC_{50} = 0.09-1.7 µM). The compound displays irreversible inhibition through catalysis of the hydrogen peroxide-dependent oxidation of PTP. It enhances insulin signaling *in vitro* and insulin tolerance in *ob/ob* mice *in vivo*. BVT 948 also inhibits several cytochrome P450 isoforms (IC_{50} < 10 µM).



Liljebris *et al* (2004) Oxidation of protein tyrosine phosphatases as a pharmaceutical mechanism of action: a study using 4-hydroxy-3,3-dimethyl-2*H*-benzo[*g*]indole-2,5(3*H*)-dione. J.Pharmacol.Exp.Ther. ***309*** 711.

Miscellaneous Signaling

2066	Anti-c-Fos Y New	Antibody recognizing c-Fos	100 µg
2131	Anti-c-Fos blocking peptide New	Blocking peptide for Cat. No. 2066	50 µg
2364	Anti-NCAM Y New	Antibody recognizing NCAM	100 µg
2324	Necrostatin-1 New	Novel inhibitor of non-apoptotic cell death (necroptosis)	10 mg
			50 mg
1984	Nogo-66 (1-40)	Competitive antagonist for Nogo-66 receptor; promotes neuron regeneration	1 mg
1741	Tocriscreen Miscellaneous Signaling	Collection of miscellaneous signaling tools	1 set

Tocriscreen Compound Libraries

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  - **Neuroscience Collection** (654 compounds)
  - **Signal Transduction Collection** (386 compounds)
- **Compound Libraries** (6-95 compounds active on a known biopharmacological system)

Signal Transduction Collection

	Cat. No.
Signal Transduction Collection (386 compounds)	1713
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Cell Cycle and Apoptosis (52 compounds)	1738
Cyclic Nucleotide Tools (22 compounds)	1735
Enzyme Inhibitors (53 compounds)	1719
Ion Channel Modulators (49 compounds)	1724
Lipid Signaling (25 compounds)	1736
Miscellaneous Signaling (12 compounds)	1741
Nitric Oxide (30 compounds)	1726
Prostanoids (22 compounds)	1729
Protein Kinase/Phosphatase Tools (67 compounds)	1737
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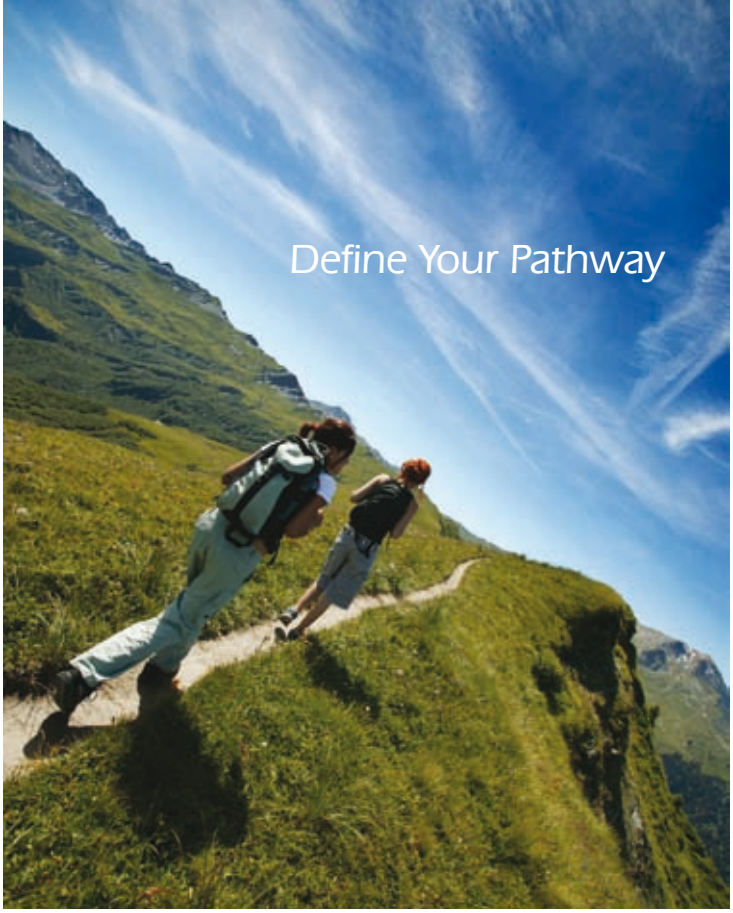

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  Compounds are pre-dissolved in DMSO at convenient stock concentrations*
- **Cost Effective**
  Test multiple compounds in smaller amounts

MAPK Cascade Inhibitor Tocriset (Cat. No. 1878)
1 set

Genistein (Cat. No. 1110); EGFR kinase inhibitor
PD 98059 (Cat. No. 1213); specific inhibitor of MAPKK/MEK
ZM 336372 (Cat. No. 1321); potent, selective c-Raf inhibitor
U0126** (Cat. No. 1144); potent, selective inhibitor of MEK1 and 2
SB 203580 (Cat. No. 1201); selective inhibitor of p38 MAPK

MAPK Inhibitor Tocriset (Cat. No. 1879)
1 set

PD 98059 (Cat. No. 1213); specific inhibitor of MAPKK/MEK
SB 203580 (Cat. No. 1202); selective inhibitor or p38 MAPK
SB 202190 (Cat. No. 1264); potent, selective inhibitor of p38 MAPK
SP 600125 (Cat. No. 1496); selective JNK inhibitor
U0126** (Cat. No. 1144); potent, selective inhibitor of MEK1 and 2

MEK Inhibitor Tocriset (Cat. No. 2243)
1 set

PD 98059 (Cat. No. 1213); specific inhibitor of MAPKK/MEK
SL 327 (Cat. No. 1969); selective inhibitor of MEK1/2; brain penetrant
U0126** (Cat. No. 1144); potent, selective inhibitor of MEK1 and 2

p38 MAPK Inhibitor Tocriset (Cat. No. 2244)
1 set

SB 202190 (Cat. No. 1264); potent, selective inhibitor of p38 MAPK
SB 203580 (Cat. No. 1202); selective inhibitor or p38 MAPK
SB 239063 (Cat. No. 1962); potent, selective inhibitor of p38 MAPK; orally active

PKA Tocriset (Cat. No. 1882)
1 set

cAMPS-Rp, triethylammonium salt (Cat. No. 1337); competitive antagonist of cAMP-induced PKA activation
8-Bromo-cAMP, sodium salt (Cat. No. 1140); cell-permeable cAMP analog; PKA activator
Forskolin (Cat. No. 1099); cell-permeable activator of adenylyl cyclase
KT 5720 (Cat. No. 1288); potent, selective inhibitor of PKA
NKH 477 (Cat. No. 1603); water-soluble analog of forskolin; activator of adenylyl cyclase

Mixed Kinase Inhibitor Tocriset (Cat. No. 1880)
1 set

GF 109203X (Cat. No. 0741); selective inhibitor of PKC
KN-62 (Cat. No. 1277); selective inhibitor of CaM kinase II
KT 5720 (Cat. No. 1288); potent, selective inhibitor of PKA
KT 5823 (Cat. No. 1289); highly selective inhibitor of PKG
Staurosporine (Cat. No. 1285); broad spectrum protein kinase inhibitor

Phosphodiesterase Inhibitor Tocriset (Cat. No. 1881)
1 set

Cilostamide (Cat. No. 0915); selective inhibitor of PDE3
Milrinone (Cat. No. 1504); potent inhibitor of PDE3
Ro 20-1724 (Cat. No. 0415); widely used PDE inhibitor; selective for PDE4
(R)-(-)-Rolipram (Cat. No. 1349); selective inhibitor of PDE4
Zardaverine (Cat. No. 1046); selective inhibitor of PDE3 and 4

*DMSO stock concentrations range from 0.1-10 mM
**U0126 (Cat. No. 1144) is supplied as a pre-weighed solid. Solubility instructions are provided to make up a 5 or 10 mM stock solution.

Further information on the Tocriset range can be found in the Tocris catalog or on www.tocris.com.

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