ENZYMES

Adenylyl cyclases (E.C. 4.6.1.1)

Overview: Adenylyl cyclase (ENSF00000000188) converts 5′-ATP to 3′,5′-adenosine monophosphate and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six transmembrane domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, Premont *et al*., 1996) and Gαs (the stimulatory G protein α subunit). Adenosine and its derivatives (e.g. 2′,5′-dideoxyadenosine), acting through the P-site, appears to be a physiological inhibitor of adenylyl cyclase activity (Tesmer *et al*., 2000). Three families of adenylyl cyclase are distinguishable: Ca^{2+}/CaM-stimulated (AC1, AC3 and AC8), Ca^{2+}-inhibitable (AC5 and AC6) and Ca^{2+}-insensitive (AC2, AC4 and AC7) forms.

Nomenclature	**AC1**	**AC2**	**AC3**	**AC4**	**AC5**
Other names	AC I	AC II, HBCA2	AC III, olfactory type	AC IV	AC V
Ensembl ID	ENSG00000164742	ENSG00000078295	ENSG00000138031	ENSG00000129467	ENSG00000173175
Endogenous activators	Ca^{2+}/CaM (Tang *et al*., 1991), PKC-evoked phosphorylation (Jacobowitz *et al*., 1993)	Gβγ (Taussig *et al*., 1993), PKC-evoked phosphorylation (Chen and Iyengar, 1993; Lustig *et al*., 1993)	Ca^{2+}/CaM (Choi *et al*., 1992), PKC-evoked phosphorylation (Jacobowitz *et al*., 1993)	Gβγ (Gao and Gilman, 1991)	PKC-evoked phosphorylation (Kawabe *et al*., 1994)
Endogenous inhibitors	Gαi (Taussig *et al*., 1994), Gαo (Taussig *et al*., 1994), Gβγ (Taussig *et al*., 1993)	—	Gαi (Taussig *et al*., 1994), RGS2 (Sinnarajah *et al*., 2001), CaM kinase II-evoked phosphorylation (Wayman *et al*., 1995)	PKC-evoked phosphorylation (Zimmermann and Taussig, 1996)	Gαi (Taussig *et al*., 1994), Ca^{2+} (Ishikawa *et al*., 1992), PKA-evoked phosphorylation (Iwami *et al*., 1995)
Selective inhibitors	—	—	—	—	NKY80 (Onda *et al*., 2001)

Nomenclature	**AC6**	**AC7**	**AC8**	**AC9**
Other names	AC VI, Ca^{2+}-inhibitable cyclase	AC VII	AC VIII	AC IX
Ensembl ID	ENSG00000174233	ENSG00000121281	ENSG00000155897	ENSG00000162104
Endogenous activators	—	PKC-evoked phosphorylation (Watson *et al*., 1994)	Ca^{2+} (Cali *et al*., 1994)	—
Endogenous inhibitors	Gαi (Taussig *et al*., 1994), Ca^{2+} (Yoshimura and Cooper, 1992), PKA-evoked phosphorylation (Chen *et al*., 1997), PKC-evoked phosphorylation (Lai *et al*., 1999)	—	—	Ca^{2+}/calcineurin (Paterson *et al*., 2000)

Nitric oxide has been proposed to inhibit AC5 and AC6 selectively (Hill *et al*., 2000), although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described (ENSG00000143199, Buck *et al*., 1999), unaffected by either Gα or Gβγ subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor (Chen *et al*., 2000).

Abbreviations: **CaM**, calmodulin; **NKH477**, 6-(3-dimethylaminopropionyl) forskolin hydrochloride; **NKY80**, 2-amino-7-(2-furanyl)-7,8-dihydro-5(6*H*)-quinazolinone; **PKA**, protein kinase A or cyclic AMP-dependent protein kinase; **PKC**, protein kinase C; **RGS2**, Regulator of G-protein signalling 2 (ENSG00000116741)

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Amino acid hydroxylases (E.C.1.14.16.–)

Overview: The amino acid hydroxylases (monooxygenases) are iron-containing enzymes which utilise molecular oxygen and tetrahydrobiopterin as co-substrate and co-factor, respectively.

Nomenclature	**L-Phenylalanine hydroxylase**	**L-Tryptophan hydroxylase**	**L-Tyrosine hydroxylase**
E.C.	1.14.16.1	1.14.16.4	1.14.16.2
Preferred abbreviation	PH	TPH	TH
Other names	Phenylalanine 4-monooxygenase	Tryptophan 5-monooxygenase	Tyrosine 3-monooxygenase
Ensembl ID	ENSG00000171759	TPH1 ENSG00000129167; TPH2 ENSG00000139287	ENSG00000180176
Product	Tyrosine	5-Hydroxytryptophan	DOPA
Selective inhibitors	α-Methylphenylalanine (Greengard *et al*., 1996), PCPA	Fenfluramine, PCPA, α-propyldopacetamide, 6-fluorotryptophan (Nicholson & Wright, 1981)	3-Chlorotyrosine, 3-iodotyrosine, α-methyltyrosine, α-propyldopacetamide

Abbreviations: **DOPA**, 3,4-dihydroxyphenylalanine; **PCPA**, 4-chlorophenylalanine

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Cyclooxygenase (E.C. 1.14.99.1)

Overview: Prostaglandin (PG) G/H synthase, most commonly referred to as cyclooxygenase (COX, (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate,hydrogen-donor : oxygen oxidoreductase) activity, catalyses the formation of PG G_2 from arachidonic acid. Hydroperoxidase activity inherent in the enzyme catalyses the formation of PGH_2 from PGG_2. COX-1 and -2 can be nonselectively inhibited by ibuprofen, ketoprofen, naproxen, indometacin and paracetamol (acetaminophen).

Nomenclature	**COX-1**	**COX-2**
Other names	Prostaglandin G_2/H_2 synthase-1	Prostaglandin G_2/H_2 synthase-2
Ensemble ID	ENSG00000095303	ENSG00000073756
Substrates	Arachidonic acid	Arachidonic acid, docosahexaenoic acid
Selective inhibitors	FR122047 (7.5, Ochi *et al*., 2000), valeroylsalicylate (Bhattacharyya *et al*., 1995)	Diclofenac (6.7), celecoxib (5.1), rofecoxib (4.3), valdecoxib, parecoxib, etoricoxib, lumiracoxib

Abbreviations: **FR122047**, 1-([4,5-bis{methoxyphenyl}-2-thazoyl]carbonyl)-4-methyl)piperazine hydrochloride

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Decarboxylases (E.C. 4.1.1.–)

Overview: The decarboxylases generate CO_2 and the indicated products from acidic substrates, requiring pyridoxal phosphate (ADC, AADC, GAD, HDC, ODC and PSDC or pyruvate (SAMDC and PSDC) as a co-factor. The activity of ODC is regulated by the presence of an antizyme (ENSF00000002504) and an ODC antizyme inhibitor (ENSF00000002504).

Nomenclature	***S*-Adenosylmethionine decarboxylase**	**L-Arginine decarboxylase**	**L-Aromatic amino-acid decarboxylase**	**Glutamic acid decarboxylase**
E.C.	4.1.1.50	4.1.1.19	4.1.1.28	4.1.1.15
Preferred abbreviation	SAMDC	ADC	AADC	GAD
Other names	—	Ornithine decarboxylase-like protein (Zhu *et al*., 2004)	DOPA decarboxylase (DDC), 5-hydroxytryptophan decarboxylase	GAD1 (GAD65), GAD2 (GAD67)
Ensembl ID	ENSG00000123505	ENSG00000142920	ENSG00000132437	ENSG00000128683, ENSG00000136750
Substrate(s)	*S*-Adenosylmethionine	L-Arginine	DOPA, L-tryptophan, 5-hydroxy-L-tryptophan	L-Glutamate, L-aspartate
Product(s)	5′-Deoxyadenosyl-(3-aminopropyl) methylsulfonium	Agmatine	5-Hydroxytryptophan, dopamine	GABA
Selective inhibitors	SAM486A (8.0; Stanek *et al*., 1993), AMA	—	Benserazide, carbidopa, 3-hydroxybenzylhydrazine, L-α-methyldopa	*S*-Allylglycine

The presence of a functional ADC activity in human tissues has been questioned (Coleman *et al*., 2004). *S*-Allylglycine is also an inhibitor of SAMDC (Pajunen *et al*., 1979).

Nomenclature	**Histidine decarboxylase**	**Ornithine decarboxylase**	**Phosphatidylserine decarboxylase**
E.C.	4.1.1.22	4.1.1.17	4.1.1.65
Preferred abbreviation	HDC	ODC	PSDC
Ensembl ID	ENSG00000140287	ENSG00000115758	ENSG00000100141
Substrate(s)	L-Histidine	L-Ornithine	Phosphatidylserine
Product	Histamine	Putrescine	Phosphatidylethanolamine
Selective inhibitors	FMH (Garbarg *et al*., 1980)	DFMO, APA	—

Abbreviations: **AMA**, S-(5′-deoxy-5′-adenosyl)-methylthioethyl-hydroxylamine; **APA**, 1-aminooxy-3-aminopropane; **DFMO**, α-difluoromethyl-L-ornithine, also known as eflornithine; **FMH**, α-fluoromethylhistidine; **SAM**, S-adenosylmethionine; **SAM486A**, 1-guanidinoimino-2,3-dihydroindene-4-carboximidamide, also known as CGP48664

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Inositol monophosphatase (E.C.3.1.3.25)

Overview: Inositol monophosphatase (IMPase, *myo*-inositol-1(or 4)-phosphate phosphohydrolase) is a magnesium-dependent homodimer which hydrolyses *myo*-inositol monophosphate to generate *myo*-inositol and phosphate. Glycerol may be a physiological phosphate acceptor. Lithium is a nonselective un-competitive inhibitor of IMPase (pK_i *ca.* 3.5, McAllister *et al*., 1992). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, McAllister *et al*., 1992), although the enzyme selectivity is not yet established.

Nomenclature	**IMPase 1**	**IMPase 2**
Other names	IMPA1	IMPA2
Ensembl ID	ENSG00000133731	ENSG00000141401
Rank order of affinity	Inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate (McAllister *et al*., 1992)	—

Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder (Sjoholt *et al*., 1997; Yoshikawa *et al*., 1997; Sjoholt *et al*., 2000).

Abbreviations: **L690330**, 1-(4-hydroxyphenoxy)ethane-1,1-bisphosphonate

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Lipoxygenases (E.C. 1.13.11.–)

Overview: The lipoxygenases (LOXs) are a structurally related family of nonheme iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. In humans, the 5*S*-(arachidonate : oxygen 5-oxidoreductase), 12*R*-(arachidonate 12-lipoxygenase, 12*R*-type), 12*S*-(arachidonate : oxygen 12-oxidoreductase), and 15*s*-(arachidonate : oxygen 15-oxidoreductase). LOXs oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5*S*-, 12*S*-, 12*R*-, or 15*S*-hydroperoxides, respectively. The epidermal lipoxygenase 3 (E-LOX) metabolises the product from the 12*R*-lipoxygenase (12*R*-HPETE) to a specific epoxyalcohol compound (Yu *et al*., 2003). Some general LOX inhibitors are NDGA and esculetin.

Nomenclature	**5-LOX**	**12*R*-LOX**	**12*S*-LOX**
E.C.	1.13.11.34	1.13.11.-	1.13.11.31
Other names	ALOX5	ALOX12B	ALOX12, platelet-type 12-lipoxygenase
Ensembl ID	ENSG00000012779	ENSG00000179477	ENSG00000108839
Substrates	Arachidonic acid	Methyl arachidonate	Arachidonic acid
Activators	FLAP	—	—
Selective inhibitors	Zileuton, CJ13610 (Fischer *et al*., 2004)	—	—

Nomenclature	**15-LOX-1**	**15-LOX-2**	**E-LOX**
E.C.	1.13.11.33	1.13.11.33	1.13.11.-
Other names	ALOX15, arachidonate ω-6 lipoxygenase	ALOX15B	Epidermis type LOX 3
Ensembl ID	ENSG00000161905	ENSG00000179593	ENSG00000179148
Substrates	Linoleic acid, arachidonic acid	Arachidonic acid	12*R*-HPETE

An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 (Furstenberger *et al*., 2002). Caffeic acid is used as a 5-lipoxygenase inhibitor, while baicalein and CDC are 12-lipoxygenase inhibitors. The specificity of these inhibitors has not been rigorously assessed with all LOX forms: baicalein, along with other flavonoids, such as fisetin and luteolin, also inhibits 15-LOX-1 (Sadik *et al*., 2003).

Abbreviations: **CDC**, cinnamyl-3,4-dihydroxy-α-cyanocinnamate; **CJ13610**, 1-carboxamido-1-(3-*S*-[4-{2-methylimididazole}-thiophenyl])-4-cyclopentylether; **esculetin**, 6,7-dihydroxycoumarin; **12*R*-HPETE**, 12*R*-hydroperoxyeicosatetraenoic acid; **FLAP**, 5-lipoxygenase-activating protein, also known as MK-886-binding protein (ENSG00000132965); **NDGA**, nordihydroguaiaretic acid

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Nitric oxide synthase (E.C. 1.14.13.39)

Overview: The nomenclature suggested by NC-IUPHAR of NOS I, II and III (see Moncada *et al*., 1997) has not gained wide acceptance. Nitric oxide synthases (NOS, L-arginine, $NADPH_2$:oxygen oxidoreductase (nitric-oxide-forming)) utilise L-arginine (not D-arginine) and molecular oxygen to generate nitric oxide and L-citrulline. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+}/calmodulin and thus appears to be constitutively active. All the three isoforms are homodimers and require tetrahydrobiopterin, flavin adenine dinucleotide, flavin mononucleotide and NADPH for catalytic activity. L-NAME is an inhibitor of all three isoforms, with an IC_{50} value in the micromolar range.

Nomenclature	**Endothelial NOS**	**Inducible NOS**	**Neuronal NOS**
Preferred abbreviation	ENOS	iNOS	nNOS
Other names	NOS III, NOS-3, ecNOS	NOS II, NOS-2	NOS I, NOS-1, brain NOS
Ensembl ID	ENSG00000164867	ENSG00000007171	ENSG00000089250
Selective inhibitors	—	1400W (8.2, Garvey *et al*., 1997), 2-amino-4-methylpyridine (7.4, Faraci *et al*., 1996), PIBTU (7.3, Garvey *et al*., 1994), NIL (5.5, Moore *et al*., 1994), aminoguanidine (Corbett & McDaniel, 1992)	3-Bromo-7NI (6.1-6.5, Bland-Ward and Moore, 1995), 7NI (5.3, Babbedge *et al*., 1993)

The reductase domain of NOS catalyses the reduction of cytochrome *c* and other redox-active dyes (Mayer & Hemmens, 1997). NADPH:O_2 oxidoreductase catalyses the formation of superoxide anion/H_2O_2 in the absence of arginine and tetrahydrobiopterin.

Abbreviations: **1400W**, *N*-(3-(aminomethyl) benzyl)acetamidine; **NADPH**, reduced nicotinamide adenosine dinucleotide phosphate; **7NI**, 7-nitroindazole; **NIL**, L-N^6-(1-iminoethyl)lysine; **PIBTU**, 13-phenylen-bis(1,2ethanediyl)bis-thiourea

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Phosphatidylcholine-specific phospholipase D (E.C. 3.1.4.4)

Overview: Phosphatidylcholine-specific phospholipase D (PLD, ENSF00000001451) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidylation reaction (Randall *et al*., 1990).

Nomenclature	**PLD1**	**PLD2**
Other names	Choline phosphatase 1	Choline phosphatase 2
Ensembl ID	ENSG00000075651	ENSG00000129219
Endogenous activators	ARF, PIP_2, RhoA, PKC-evoked phosphorylation (Hammond *et al*., 1997)	ARF, PIP_2 (Lopez *et al*., 1998), oleic acid (Sarri *et al*., 2003)

A lysophospholipase D activity (ENSG00000136960, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al*., 2003). Additionally, an *N*-acylethanolamine-specific phospholipase D (NAPE-PLD, ENSG00000161048) has recently been characterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide (Okamoto *et al*., 2004). This enzyme activity appears to be enhanced by polyamines in the physiological range (Liu *et al*., 2002) and fails to transphosphatidylate with alcohols (Petersen & Hansen, 1999).

Abbreviations: **ARF**, ADP-ribosylation factor; **NAPE-PLD**, *N*-acylethanolamine-specific phospholipase D; **PIP_2**, phosphatidylinositol 4,5-bisphosphate

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Phosphodiesterases, 3′,5′-cyclic nucleotide (E.C.3.1.4.17)

Overview: 3′,5′-Cyclic nucleotide phosphodiesterases (PDEs, 3′,5′-cyclic-nucleotide 5’-nucleotidohydrolase) catalyse the hydrolysis of a 3′,5′-cyclic nucleotide (usually cyclic AMP or cyclic GMP). IBMX is a nonselective inhibitor with an IC_{50} value in the millimolar range for all isoforms except PDE 8A, 8B and 9A. A 2′,3′-cyclic nucleotide 3′-phosphodiesterase (E.C. 3.1.4.37 CNPase) activity is associated with myelin formation in the development of the CNS.

Nomenclature	**PDE1A**	**PDE1B**	**PDE1C**	**PDE2A**
Other names	PDE I	PDE I	PDE I	PDE II, cGMP- stimulated cAMP-PDE, CGS-PDE
Ensembl ID	ENSG00000115252	ENSG00000123360	ENSG00000154678	SwissProt O00408
Rank order of affinity	cGMP > cAMP	cGMP > cAMP	cGMP = cAMP	cAMP≫cGMP
Activators	Ca^{2+}/CaM	Ca^{2+}/CaM	Ca^{2+}/CaM	cGMP
Selective inhibitors	SCH51866 (7.2, Vemulapalli *et al*., 1996), vinpocetine (5.1, Loughney *et al*., 1996)	SCH51866 (7.2, Vemulapalli *et al*., 1996)	SCH51866 (7.2, Vemulapalli *et al*., 1996), vinpocetine (4.3, Loughney *et al*., 1996)	BAY607550 (8.3–8.8, Boess *et al*., 2004), EHNA (5.3, Michie *et al*., 1996)

PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4).

Nomenclature	**PDE3A**	**PDE3B**
Other names	PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE A	PDE III, cGMP-inhibited cAMP-PDE, CGI-PDE B
Ensembl ID	ENSG00000172572	ENSG00000152270
Selective inhibitors	Cilostamide (7.5, Sudo *et al*., 2000), milrinone (6.3, Sudo *et al*., 2000), cGMP	Cilostamide (7.3, Sudo *et al*., 2000), milrinone (6.0, Sudo *et al*., 2000), cGMP

PDE3A and PDE3B are membrane-bound.

Nomenclature	**PDE4A**	**PDE4B**	**PDE4C**	**PDE4D**
Other names	PDE IV	PDE IV	PDE IV	PDE IV
Ensembl ID	ENSG00000065989	ENSG00000184588	ENSG00000105650	ENSG00000113448
Rank order of affinity	cAMP≫cGMP	cAMP≫cGMP	cAMP≫cGMP	cAMP≫cGMP
Activators	—	—	—	PKA-mediated phosphorylation (Houslay & Adams, 2003)
Selective inhibitors	Rolipram (9.0, Wang *et al*., 1997), YM976 (8.3, Aoki *et al*., 2000), Ro201724 (6.5, Wang *et al*., 1997)	Rolipram (9.0, Wang *et al*., 1997), Ro201724 (6.4, Wang *et al*., 1997)	Rolipram (6.5, Wang *et al*., 1997), Ro201724 (5.4, Wang *et al*., 1997)	Rolipram (7.2, Wang *et al*., 1997), Ro201724 (6.2, Wang *et al*., 1997)

PDE4 isoforms are essentially cAMP specific. The potency of YM976 at other members of the PDE4 family has not been reported. PDE4B–D long forms are inhibited by extracellular signal-regulated kinase (ERK)-mediated phosphorylation (Hoffmann *et al*., 1998; Hoffmann *et al*., 1999). PDE4A–D splice variants can be membrane-bound or cytosolic (Houslay & Adams, 2003). PDE4 isoforms may be labelled with [^{3}H]-rolipram.

Nomenclature	**PDE5A**	**PDE7A**	**PDE7B**	**PDE8A**	**PDE8B**
Other names	PDE V, cGMP-specific PDE	HCP1	—	High-affinity cAMP-specific and IBMX-insensitive PDE	—
Ensembl ID	ENSG00000138735	ENSG00000104732	ENSG00000171408	ENSG00000073417	ENSG00000113231
Rank order of affinity	cGMP > cAMP	cAMP≫cGMP (Michaeli *et al*., 1993)	cAMP≫cGMP (Gardner *et al*., 2000)	cAMP≫cGMP (Fisher *et al*., 1998a)	cAMP≫cGMP (Hayashi *et al*., 1998)
Activators	PKA (Corbin *et al*., 2000), PKG (Corbin *et al*., 2000)	—	—	—	—
Selective inhibitors	T0156 (9.5, Mochida *et al*., 2002), sildenafil (9.0, Turko *et al*., 1999), SCH51866 (7.2, Vemulapalli *et al*., 1996), zaprinast (6.8, Turko *et al*., 1999)	BRL50481 (6.7, Smith *et al*., 2004)	Dipyridamole (5.7–6.0, Gardner *et al*., 2000; Sasaki *et al*., 2000), SCH51866 (5.8, Sasaki *et al*., 2000)	Dipyridamole (5.1, Fisher *et al*., 1998a)	Dipyridamole (4.3, Hayashi *et al*., 1998)

PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively. BRL50481 appears not to have been examined as an inhibitor of PDE7B.

Nomenclature	**PDE9A**	**PDE10A**	**PDE11A**
Ensembl ID	ENSG00000160191	ENSG00000112541	ENSG00000128655
Substrate specificity	cGMP≫cAMP (Fisher *et al*., 1998b)	cAMP, cGMP (Fujishige *et al*., 1999)	cAMP, cGMP (Fawcett *et al*., 2000)
Selective inhibitors	SCH51866 (5.8, Fisher *et al*., 1998b), zaprinast (4.5, Fisher *et al*., 1998b)	—	—

Nomenclature	**PDE6A**	**PDE6B**	**PDE6C**	**PDE6D**	**PDE6G**	**PDE6H**
Other names	cGMP-PDE α, PDE V-b1	cGMP-PDE β	cGMP-PDE α, PDEA2	cGMP-PDE δ	cGMP-PDE γ	cGMP-PDE γ
Ensembl ID	ENSG00000132915	ENSG00000133256	ENSG00000095464	ENSG00000156973	ENSG00000185527	ENSG00000139053

PDE6 is a membrane-bound tetramer composed of two catalytic chains (PDE6A or PDE6C and PDE6B), an inhibitory chain (PDE6G or PDE6H) and the PDE6D chain. The enzyme is essentially cGMP specific and is activated by the α-subunit of transducin (G_t) and inhibited by sildenafil, zaprinast and dipyridamole with potencies lower than those observed for PDE5A. Defects in PDE6B are a cause of retinitis pigmentosa and congenital stationary night blindness.

Abbreviations: **BAY607550**, 2-(3,4-dimethoxybenzyl)-7-{(1R)-1-[(1R)-1-hydroxyethyl]-4-phenylbutyl}-5-methylimidazo[5,1-f][1,2,4]triazin-4(3*H*)-one; **BRL50481**, 5-nitro-2,*N*,*N*-trimethylbenzenesulfonamide; **EHNA**, *erythro*-9-(2-hydroxy-3-nonyl)adenine; **PKA**, cyclic AMP-dependent protein kinase; **PKG**, cyclic GMP-dependent protein kinase; **Ro201724**, 4-(3-butoxy-4-methoxyphenyl)methyl-2-imidazolidone; **YM976**, (4-[3-chlorophenyl]-1,7-diethylpyrido[2,3-d]pyrimidin-2(1*H*)-one); **SCH51866**, *cis*-5,6*a*,7,8,9,9*a*-hexahydro-2-(4-[trifluoromethyl]phenylmethyl)-5-methyl-cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one

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Phosphoinositide-specific phospholipase C (E.C. 3.1.4.11)

Overview: Phosphoinositide-specific phospholipase C (PLC) catalyses the hydrolysis of phosphatidylinositol (4,5)-bisphosphate to inositol (1,4,5)-trisphosphate and 1,2-diacylglycerol, each of which have major second messenger functions. Two domains, X and Y, essential for catalytic activity, are conserved in the different forms of PLC. Isoforms of PLC-β (ENSF00000000466) are activated primarily by 7TM receptors through members of the $G_{q/11}$ family of G proteins. The receptor-mediated activation of PLC-γ involves their phosphorylation by tyrosine kinases in response to activation of a variety of growth factor receptors and immune system receptors. PLC-ε1 may represent a point of convergence of signalling via both 7TM and catalytic receptors. Ca^{2+} ions are required for catalytic activity of PLC isoforms and have been suggested to be the major physiological form of regulation of PLC-δ activity. PLC has been suggested to be activated non-selectively by the small molecule *m*-3M3FBS (Bae *et al*., 2003), although this mechanism of action has been questioned (Krjukova *et al*., 2004). The aminosteroid U73122 has been described as an inhibitor of phosphoinositide-specific PLC (Smith *et al*., 1990), although its selectivity among the isoforms is untested and it has been reported to occupy the H_1 histamine receptor (Hughes *et al*., 2000).

Nomenclature	**β1**	**β2**	**β3**	**β4**
Other names	PLC-I, PLC-154, KIAA0581	—	—	—
Ensembl ID	ENSG00000182621	ENSG00000137841	ENSG00000149782	ENSG00000101333
Endogenous activators	Gαq (Smrcka *et al*., 1991; Hepler *et al*., 1993), Gα11 (Hepler *et al*., 1993), G$\beta\gamma$ (Park *et al*., 1993)	Gα16 (Lee *et al*., 1992), G$\beta\gamma$ (Camps *et al*., 1992; Park *et al*., 1993)	Gαq (Lee *et al*., 1992), G$\beta\gamma$ (Carozzi *et al*., 1993; Park *et al*., 1993)	Gαq (Jhon *et al*., 1993)

Nomenclature	**γ1**	**γ2**	**δ1**	**δ3**	**δ4**
Other names	PLC-II, PLC-148	PLC-IV	PLC-III	—	—
Ensembl ID	ENSG00000124181	ENSG00000197943	ENSG00000187091	ENSG00000161714	ENSG00000115556
Endogenous activators	$PtdIns(3,4,5)P_3$ (Bae *et al*., 1998)	$PtdIns(3,4,5)P_3$ (Bae *et al*., 1998)	Transglutaminase II (Murthy *et al*., 1999), p122-RhoGAP (Homma & Emori, 1995), spermine (Haber *et al*., 1991), G$\beta\gamma$ (Park *et al*., 1993)	—	—
Inhibitors	—	—	Sphingomyelin (Pawelczyk & Lowenstein, 1992)	—	—

PLC-δ2 has been cloned from bovine sources (Meldrum *et al*., 1991).

Nomenclature	**ε1**	**ζ1**	**η1**	**η2**
Other names	Pancreas-enriched PLC	—	—	—
Ensembl/GenBank ID	ENSG00000138193	ENSG00000139151	AY691170 (Hwang *et al*., 2005)	DQ176850 (Zhou *et al*., 2005)
Endogenous activators	Ras (Song *et al*., 2001), Rho (Wing *et al*., 2003)	—	—	G$\beta\gamma$ (Zhou *et al*., 2005)

A series of PLC-like proteins (PLCL1 ENSG00000115896; PLCL2 ENSG00000154822 and PLCL3 ENSG00000114805) form a family (ENSF00000000386) with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity.

Abbreviations: ***m*-3M3FBS**, 2,4,6-trimethyl-*N*-(*meta*-3-trifluoromethylphenyl)-benzenesulphonamide; **PtdIns (3,4,5)P_3**, phosphatidylinositol (3,4,5)-trisphosphate; **U73122**, 1-(6-[{(17β)-3-methoxyestra-1,3,5[10]-trien-17-yl}amino]hexyl)-1*H*-pyrrole-2,5-dione

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Soluble guanylyl cyclase (E.C. 4.6.1.2)

Overview: Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)) is a heterodimer comprising α and β chains, both of which have two subtypes in man (predominantly $\alpha1\beta1$; see Zabel *et al*., 1998). A haem group is associated with the β chain and is the target for the endogenous ligand nitric oxide ($NO^{\bullet}$), and, potentially, carbon monoxide (Friebe *et al*., 1996). The enzyme converts guanosine-5′-triphosphate (GTP) to the intracellular second messenger 3′,5′-guanosine monophosphate (cGMP).

Nomenclature	**Soluble guanylyl cyclase**
Preferred abbreviation	sGC
Ensembl ID	$\alpha1$ ENSG00000164116; $\alpha2$ ENSG00000152402; $\beta1$ ENSG00000061918; $\beta2$ ENSG00000123201
Selective activators	$NO^{\bullet}$, YC1 (Friebe *et al*., 1996), BAY412272 (Stasch *et al*., 2001), BAY582667 (Stasch *et al*., 2002)
Selective inhibitors	ODQ (7.5; Garthwaite *et al*., 1995)

ODQ also shows activity at other haem-containing proteins (Feelisch *et al*., 1999), while YC1 may also inhibit cGMP-hydrolysing phosphodiesterases (Friebe *et al*. 1998).

Abbreviations: **BAY412272**, 5-cyclopropyl-2-[1-(2-fluoro-benzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-pyrimidin-4-ylamine); **BAY582667**, 4-([4-carboxybutyl][2-{(4-phenethylbenzyl)oxy}phenethyl]amino)methyl(benzoic)acid; **ODQ**, 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one; **YC1**, 3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole HMR1766

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