



University of Dundee

The Concise Guide to PHARMACOLOGY 2015/16

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monophosphatase only in the presence of high substrate concentrations. Some inhibitors are irreversible, including a group known as suicide substrates, which bind to the ligand recognition site and then couple covalently to the enzyme. It is beyond the scope of the Guide to give mechanistic information about the inhibitors described, although generally this information is avail-

able from the indicated literature.

Many enzymes require additional entities for functional activity. Some of these are used in the catalytic steps, while others promote a particular conformational change. Co-factors are tightly bound to the enzyme and include metal ions and heme groups. Co-enzymes are typically small molecules which accept or donate

functional groups to assist in the enzymatic reaction. Examples include ATP, NAD, NADP and S-adenosylmethionine, as well as a number of vitamins, such as riboflavin (vitamin B1) and thiamine (vitamin B2). Where co-factors/co-enzymes have been identified, the Guide indicates their involvement.

Family structure

This is a complete listing of enzyme families included in the online IUPHAR/BPS Guide to PHARMACOLOGY database. Summary information is provided for a subset of enzyme families (those with page numbers) in the tables below. Family members judged to be of significant pharmacological interest have been included, with further enzymes listed in the database.

6028	Protein Kinases (EC 2.7.x.x)	–	Bromodomain kinase (BRDK) family	–	family
–	AGC: Containing PKA, PKC, PKG families	–	G11 family	–	MAPKAPK subfamily
–	DMPK family	–	Phosphatidylinositol 3' kinase-related kinases (PIKK) family	–	MKN subfamily
–	GEK subfamily	–	ATR subfamily	–	Myosin Light Chain Kinase (MLCK) family
–	Other DMPK family kinases	–	FRAP subfamily	–	Phosphorylase kinase (PHK) family
6028	Rho kinase	6030	SMG1 subfamily	–	PIM family
–	G protein-coupled receptor kinases	–	TRRAP subfamily	–	Protein kinase D (PKD) family
–	BARK/GRK2 subfamily	–	Other PIKK family kinases	–	PSK family
–	GRK1/3 subfamily	–	RIO family	–	RAD53 family
–	MAST family	–	RIO1 subfamily	–	Trbl family
–	NDR family	–	RIO2 subfamily	–	Trio family
–	PDK1 family	–	RIO3 subfamily	–	CK1: Casein kinase 1
–	Protein kinase A	–	PDHK family	–	Casein kinase 1 (CK1) family
–	Akt (Protein kinase B)	–	Pyruvate dehydrogenase kinase (PDHK) family	–	Tau tubulin kinase (TTBK) family
6029	Protein kinase C (PKC)	–	TAF1 family	–	Vaccinia related kinase (VRK) family
6029	Alpha subfamily	–	TIF1 family	–	CMGC: Containing CDK, MAPK, GSK3, CLK families
6029	Delta subfamily	–	CAMK: Calcium/calmodulin-dependent protein kinases	–	CLK family
6030	Eta subfamily	–	CAMK-like (CAMKL) family	–	Cyclin-dependent kinase (CDK) family
–	Iota subfamily	–	AMPK subfamily	6031	CCRK subfamily
–	Protein kinase G (PKG)	–	BRSK subfamily	–	CDK1 subfamily
–	Protein kinase N (PKN) family	–	CHK1 subfamily	–	CDK4 subfamily
–	RSK family	–	HUNK subfamily	–	CDK5 subfamily
–	MSK subfamily	–	LKB subfamily	–	CDK7 subfamily
–	p70 subfamily	–	MARK subfamily	–	CDK8 subfamily
–	RSK subfamily	–	MELK subfamily	–	CDK9 subfamily
–	RSKR subfamily	–	NIM1 subfamily	–	CDK10 subfamily
–	RSKL family	–	NuaK subfamily	–	CRK7 subfamily
–	SGK family	–	PASK subfamily	–	PITSLRE subfamily
–	YANK family	–	QIK subfamily	–	TAIRE subfamily
–	Atypical	–	SNRK subfamily	–	Cyclin-dependent kinase-like (CDKL) family
–	ABC1 family	–	CAMK-unique family	–	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase (DYRK) family
–	ABC1-A subfamily	–	CASK family	–	Dyrk1 subfamily
–	ABC1-B subfamily	–	DCAMKL family	–	Dyrk2 subfamily
–	Alpha kinase family	–	Death-associated kinase (DAPK) family	–	HIPK subfamily
–	ChaK subfamily	–	MAPK-Activated Protein Kinase (MAPKAPK)	–	PRP4 subfamily
–	eEF2K subfamily	–		–	Glycogen synthase kinase (GSK) family
–	Other alpha kinase family kinases	–		–	
–	BCR family	–		–	

6031	GSK subfamily		20 kinases	–	C54: Aut2 peptidase
–	Mitogen-activated protein kinases (MAP kinases)	6032	STE7 family	–	CD: Cysteine (C) Peptidases
–	ERK subfamily	–	STE11 family	–	C13: Legumain
–	Erk7 subfamily	–	STE20 family	6037	C14: Caspase
–	JNK subfamily	–	FRAY subfamily	–	CE: Cysteine (C) Peptidases
–	p38 subfamily	–	MSN subfamily	–	C48: Ulp1 endopeptidase
–	nmo subfamily	–	NinaC subfamily	–	M-: Metallo (M) Peptidases
–	RCK family	–	PAKA subfamily	–	M79: Prenyl protease 2
–	SRPK family	–	PAKB subfamily	–	MA: Metallo (M) Peptidases
–	Other protein kinases	–	STLK subfamily	6037	M1: Aminopeptidase N
–	CAMKK family	–	TAO subfamily	6038	M2: Angiotensin-converting (ACE and ACE2)
–	Meta subfamily	–	STE20 family	6038	M10: Matrix metalloproteinase
–	Aurora kinase (Aur) family	–	STE-unique family	6039	M12: Astacin/Adamalysin
–	Bub family	–	TK: Tyrosine kinase	–	M13: Neprilysin
–	Bud32 family	6033	Abl family	–	M49: Dipeptidyl-peptidase III
–	Casein kinase 2 (CK2) family	6033	Ack family	–	MC: Metallo (M) Peptidases
–	CDC7 family	–	Csk family	–	M14: Carboxypeptidase A
–	Haspin family	–	Fak family	–	ME: Metallo (M) Peptidases
–	IKK family	–	Fer family	–	M16: Pitrilysin
–	IRE family	6034	Janus kinase (JakA) family	–	MF: Metallo (M) Peptidases
–	MOS family	6034	Src family	–	M17: Leucyl aminopeptidase
–	NAK family	–	Syk family	–	MG: Metallo (M) Peptidases
–	NIMA (never in mitosis gene a)- related kinase (NEK) family	6035	Tec family	–	M24: Methionyl aminopeptidase
–	NKF1 family	–	TKL: Tyrosine kinase-like	–	MH: Metallo (M) Peptidases
–	NKF2 family	–	Interleukin-1 receptor-associated kinase (IRAK) family	–	M18: Aminopeptidase I
–	NKF4 family	–	Leucine-rich repeat kinase (LRRK) family	6039	M20: Carnosine dipeptidase
–	NKF5 family	–	LIM domain kinase (LISK) family	–	M28: Aminopeptidase Y
–	NRBB family	–		6040	MJ: Metallo (M) Peptidases
–	Numb-associated kinase (NAK) family	–	LIMK subfamily	–	M19: Membrane dipeptidase
–	Other-unique family	–	TESK subfamily	–	MP: Metallo (M) Peptidases
6032	Polo-like kinase (PLK) family	–	Mixed Lineage Kinase (MLK) family	–	M67: PSMD14 peptidase
–	PEK family	–	HH498 subfamily	–	PA: Serine (S) Peptidases
–	GCN2 subfamily	–	ILK subfamily	6040	S1: Chymotrypsin
–	PEK subfamily	–	LZK subfamily	–	PB: Threonine (T) Peptidases
–	Other PEK family kinases	–	MLK subfamily	6041	T1: Proteasome
–	Sgk493 family	–	TAK1 subfamily	–	T2: Glycosylasparaginase precursor
–	Slob family	–	RAF family	–	PC: Cysteine (C) Peptidases
–	TBCK family	6035	Receptor interacting protein kinase (RIPK) family	–	C26: Gamma-glutamyl hydrolase
–	TOPK family	–	TKL-unique family	6042	SB: Serine (S) Peptidases
–	Tousled-like kinase (TLK) family	–	Peptidases and proteinases	–	S8: Subtilisin
–	TTK family	–	AA: Aspartic (A) Peptidases	6042	SC: Serine (S) Peptidases
–	Unc-51-like kinase (ULK) family	6036	A1: Pepsin	–	S9: Prolyl oligopeptidase
–	VPS15 family	6036	AD: Aspartic (A) Peptidases	–	S10: Carboxypeptidase Y
–	WEE family	–	A22: Presenilin	–	S28: Lysosomal Pro-Xaa carboxypeptidase
–	Wnk family	6037	CA: Cysteine (C) Peptidases	–	S33: prolyl aminopeptidase
–	Miscellaneous protein kinases	–	C1: Papain	6042	Acetylcholine turnover
–	actin-binding proteins ADF family	–	C2: Calpain	6044	Adenosine turnover
–	Twinfilin subfamily	–	C12: Ubiquitin C-terminal hydrolase	6045	Amino acid hydroxylases
–	SCY1 family	–	C19: Ubiquitin-specific protease	6046	L-Arginine turnover
–	Hexokinases	–		6047	Arginase
–	STE: Homologs of yeast Sterile 7, Sterile 11, Sterile	–			

6047	Arginine:glycine amidinotransferase	6069	Cytochrome P450	6091	Haem oxygenase
6047	Dimethylarginine dimethylaminohydrolases	6069	CYP1 family	6092	Hydrogen sulphide synthesis
6048	Nitric oxide synthases	6070	CYP2 family	6093	Hydrolases
6048	Carboxylases and decarboxylases	6070	CYP3 family	6093	Inositol phosphate turnover
6049	Carboxylases	6071	CYP4 family	6094	Inositol 1,4,5-trisphosphate 3-kinases
6050	Decarboxylases	6072	CYP5, CYP7 and CYP8 families	6094	Inositol polyphosphate phosphatases
6052	Catecholamine turnover	6072	CYP11, CYP17, CYP19, CYP20 and CYP21 families	6094	Inositol monophosphatase
6055	Ceramide turnover	6073	CYP24, CYP26 and CYP27 families	6095	Lanosterol biosynthesis pathway
6055	Serine palmitoyltransferase	6074	CYP39, CYP46 and CYP51 families	6097	Nucleoside synthesis and metabolism
-	3-ketodihydrospingosine reductase	6076	Eicosanoid turnover	6099	Sphingosine 1-phosphate turnover
6056	Ceramide synthase	6075	Endocannabinoid turnover	6100	Sphingosine kinase
6057	Sphingolipid Δ^4 -desaturase	6077	Cyclooxygenase	6100	Sphingosine 1-phosphate phosphatase
6058	Sphingomyelin synthase	6077	Prostaglandin synthases	6101	Sphingosine 1-phosphate lyase
6058	Sphingomyelin phosphodiesterase	6079	Lipoxygenases	6101	Thyroid hormone turnover
6059	Neutral sphingomyelinase coupling factors	6080	Leukotriene and lipoxin metabolism	-	1.4.3.13 Lysyl oxidases
6059	Ceramide glucosyltransferase	6081	GABA turnover	-	1.13.11.- Dioxygenases
6060	Acid ceramidase	6082	Glycerophospholipid turnover	6103	1.14.11.29 2-oxoglutarate oxygenases
6060	Neutral ceramidases	-	Lipid modifying kinases	6103	transferases
6061	Alkaline ceramidases	6083	1-phosphatidylinositol 4-kinase family	-	2.3.-.- Acyltransferases
6061	Ceramide kinase	6083	Phosphatidylinositol-4-phosphate 3-kinase family	6103	2.4.2.30 poly(ADP-ribose)polymerases
6062	Chromatin modifying enzymes	6084	Phosphatidylinositol 3-kinase family	6104	2.5.1.58 Protein farnesyltransferase
-	Enzymatic bromodomain-containing proteins	6084	Phosphatidylinositol-4,5-bisphosphate 3-kinase family	-	3.1.-.- Ester bond enzymes
-	Bromodomain kinase (BRDK) family	6085	1-phosphatidylinositol-3-phosphate 5-kinase family	-	3.1.1.- Carboxylic Ester Hydrolases
-	TAF1 family	6085	Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)	-	3.2.1.- Glycosidases
-	TIF1 family	6086	Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)	-	3.4.21.46 Complement factor D
-	1.14.11.- Histone demethylases	6100	Sphingosine kinase	6062	3.5.1.- Histone deacetylases (HDACs)
-	2.1.1.43 Histone methyltransferases (HMTs)	6087	Phosphoinositide-specific phospholipase C	6104	3.5.3.15 Peptidyl arginine deiminases (PADI)
-	2.3.1.48 Histone acetyltransferases (HATs)	6088	Phospholipase A ₂	-	3.6.5.2 Small monomeric GTPases
-	3.6.1.3 ATPases	6089	Phosphatidylcholine-specific phospholipase D	6104	RAS subfamily
6062	2.1.1.- Protein arginine N-methyltransferases	6090	Lipid phosphate phosphatases	6105	4.2.1.1 Carbonate dehydratases
6062	3.5.1.- Histone deacetylases (HDACs)	6082	Phosphatidylinositol kinases	-	5.-.-.- Isomerases
6063	Cyclic nucleotide turnover			-	5.2.-.- Cis-trans-isomerases
6063	Adenylyl cyclases			6105	5.99.1.2 DNA Topoisomerases
6064	Soluble guanylyl cyclase				
6065	Exchange protein activated by cyclic AMP (Epac)				
6066	Phosphodiesterases, 3',5'-cyclic nucleotide				

Protein Kinases (EC 2.7.x.x)

Enzymes → Kinases (EC 2.7.x.x)

Overview: Protein kinases (E.C. 2.7.11.-) use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Analysis of the human genome suggests the presence of 518 protein kinases in man, with over 100 protein kinase-like pseudo-

genes [313]. It is beyond the scope of the Concise Guide to list all these protein kinase activities; the full listing may be seen at [www.GuidetoPHARMACOLOGY.org](http://www.guidetopharmacology.org).

Most inhibitors of these enzymes have been assessed in cell-free

investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site [103].

Further Reading

Eglen R *et al.* (2011) Drug discovery and the human kinome: recent trends. *Pharmacol. Ther.* **130**: 144-56 [PMID:21256157]

Graves LM *et al.* (2013) The dynamic nature of the kinome. *Biochem. J.* **450**: 1-8 [PMID:23343193]

Liu Q *et al.* (2013) Developing irreversible inhibitors of the protein kinase cysteinome. *Chem. Biol.* **20**: 146-59 [PMID:23438744]

Martin KJ *et al.* (2012) Selective kinase inhibitors as tools for neuroscience research. *Neuropharma-*

cology **63**: 1227-37 [PMID:22846224]

Tarrant MK *et al.* (2009) The chemical biology of protein phosphorylation. *Annu. Rev. Biochem.* **78**: 797-825 [PMID:19489734]

Wu-Zhang AX *et al.* (2013) Protein kinase C pharmacology: refining the toolbox. *Biochem. J.* **452**: 195-209 [PMID:23662807]

Rho kinase

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → DMPK family → Rho kinase

Overview: Rho kinase (also known as P160ROCK, Rho-activated kinase) is activated by members of the Rho small G protein family, which are activated by GTP exchange factors, such as [ARHGEF1](#) (Q92888, p115-RhoGEF), which in turn may be activated by G $\alpha_{12/13}$ subunits [269].

Nomenclature	Rho-associated, coiled-coil containing protein kinase 1	Rho-associated, coiled-coil containing protein kinase 2
Systematic nomenclature	ROCK1	ROCK2
Common abbreviation	Rho kinase 1	Rho kinase 2
HGNC, UniProt	ROCK1 , Q13464	ROCK2 , O75116
EC number	2.7.11.1	2.7.11.1
Inhibitors	RKI-1447 (pIC ₅₀ >9) [387], Y27632 (pIC ₅₀ 7.3) [529], fasudil (pK _i 7) [403], Y27632 (pK _i 6.8) [496], fasudil (pIC ₅₀ 5.5) [403]	RKI-1447 (pIC ₅₀ >9) [387], compound 11d [DOI: 10.1039/c0md00194e] (pIC ₅₀ >9) [77], GSK269962A (pIC ₅₀ 8.4) [118], compound 32 [PMID: 20471253] (pIC ₅₀ 8.4) [45], compound 22 [PMID: 20462760] (pIC ₅₀ 7.7) [529], Y27632 (pIC ₅₀ 7.2) [529], Y27632 (pK _i 6.8) [496], fasudil (pIC ₅₀ 5.9) [403]
Selective inhibitors	GSK269962A (pIC ₅₀ 8.8) [118]	–

Protein kinase C (PKC)

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC)

Overview: Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl- β -phorbol acetate (TPA, also known as **phorbol 12-myristate 13-acetate**).

Classical protein kinase C isoforms: **PKC α** , **PKC β** , **PKC γ** . Mem-

bers of the classical protein kinase C family are activated by **Ca²⁺** and diacylglycerol, and may be inhibited by **GF109203X**, **calphostin C**, **GÖ 6983**, **chelerythrine** and **Ro31-8220**.

Novel protein kinase C isoforms: **PKC δ** , **PKC ϵ** , **PKC η** , **PKC θ** and

PKC μ . Members of the classical protein kinase C family are activated by diacylglycerol and may be inhibited by **calphostin C**, **GÖ 6983** and **chelerythrine**.

Atypical protein kinase C isoforms: **PKC ι** , **PKC ζ** .

Alpha subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) → Alpha subfamily

Nomenclature	protein kinase C, beta	protein kinase C, gamma
Common abbreviation	PKC β	PKC γ
HGNC, UniProt	PRKCB , P05771	PRKCG , P05129
EC number	2.7.11.13	2.7.11.13
Inhibitors	sotrastaurin (pIC ₅₀ 8.7) [506], GÖ 6983 (pIC ₅₀ 8.1) [183], GF109203X (pIC ₅₀ 7.8) [490] – Bovine, 7-hydroxystaurosporine (pIC ₅₀ 7.5) [431]	GÖ 6983 (pIC ₅₀ 8.2) [183], 7-hydroxystaurosporine (pIC ₅₀ 7.5) [431]
Selective inhibitors	ruboxistaurin (pIC ₅₀ 8.2) [238], enzastaurin (pIC ₅₀ 7.5) [132], CGP53353 (pIC ₅₀ 6.4) [70]	–

Delta subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) → Delta subfamily

Nomenclature	protein kinase C, alpha	protein kinase C, delta
Common abbreviation	PKC α	PKC δ
HGNC, UniProt	PRKCA , P17252	PRKCD , Q05655
EC number	2.7.11.13	2.7.11.13
Activators	–	ingenol mebutate (pK _i 9.4) [252]

(continued)

Nomenclature

protein kinase C, alpha

protein kinase C, delta

Inhibitors

sotrastaurin (pIC₅₀ 8.7) [506], Gö 6983 (pIC₅₀ 8.1) [183], 7-hydroxystaurosporine (pIC₅₀ 7.5) [431]

sotrastaurin (pIC₅₀ 8.9) [506], Gö 6983 (pIC₅₀ 8) [183]

Eta subfamily

Enzymes → Kinases (EC 2.7.x.x) → AGC: Containing PKA, PKG, PKC families → Protein kinase C (PKC) → Eta subfamily

Nomenclature

protein kinase C, epsilon

Common abbreviation

PKC ϵ

HGNC, UniProt

PRKCE, Q02156

EC number

2.7.11.13

Inhibitors

sotrastaurin (pIC₅₀ 8.2) [506]

FRAP subfamily

Enzymes → Kinases (EC 2.7.x.x) → Atypical → Phosphatidylinositol 3' kinase-related kinases (PIKK) family → FRAP subfamily

Nomenclature

mechanistic target of rapamycin (serine/threonine kinase)

Common abbreviation

mTOR

HGNC, UniProt

MTOR, P42345

EC number

2.7.11.1

Inhibitors

ridaforolimus (pIC₅₀ 9.7) [408], torin 1 (pIC₅₀ 9.5) [291], INK-128 (pIC₅₀ 9) [219], INK-128 (pK_i 8.9) [219], gedatolisib (pIC₅₀ 8.8) [500], dactolisib (pIC₅₀ 8.2) [310], PP-242 (pIC₅₀ 8.1) [14], PP121 (pIC₅₀ 8) [14], XL388 (pIC₅₀ 8) [472], PF-04691502 (pK_i 7.8) [290], apitolisib (pK_i 7.8) [467]

Selective inhibitors

everolimus (pIC₅₀ 8.7) [427], temsirolimus (pIC₅₀ 5.8) [266]

CDK4 subfamily

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Cyclin-dependent kinase (CDK) family → CDK4 subfamily

Nomenclature	cyclin-dependent kinase 4	cyclin-dependent kinase 6
Common abbreviation	CDK4	CDK6
HGNC, UniProt	CDK4 , P11802	CDK6 , Q00534
EC number	2.7.11.22	2.7.11.22
Inhibitors	R547 (pK _i 9) [107], palbociclib (pIC ₅₀ 8) [151], Ro-0505124 (pIC ₅₀ 7.7) [115], riviciclib (pIC ₅₀ 7.2) [246], alvocidib (pK _i 7.2) [64]	palbociclib (pIC ₅₀ 7.8) [151]

GSK subfamily

Enzymes → Kinases (EC 2.7.x.x) → CMGC: Containing CDK, MAPK, GSK3, CLK families → Glycogen synthase kinase (GSK) family → GSK subfamily

Nomenclature	glycogen synthase kinase 3 beta
Common abbreviation	GSK3B
HGNC, UniProt	GSK3B , P49841
EC number	2.7.11.26
Inhibitors	CHIR-98014 (pIC ₅₀ 9.2) [407], LY2090314 (pIC ₅₀ 9) [125], CHIR-99021 (pIC ₅₀ 8.2) [407], SB 216763 (pIC ₅₀ ~8.1) [88], 1-azakenpaullone (pIC ₅₀ 7.7) [272], SB-415286 (pIC ₅₀ ~7.4) [88], IM-12 (pIC ₅₀ 7.3) [424]
Selective inhibitors	AZD2858 (pK _i 8.3) [29]
Comments	Due to its Tau phosphorylating activity, small molecule inhibitors of GSK-3β are being investigated as potential treatments for Alzheimer's disease (AD) [29]. GSK-3β also plays a role in canonical Wnt pathway signalling, the normal activity of which is crucial for the maintenance of normal bone mass. It is hypothesised that small molecule inhibitors of GSK-3β may provide effective therapeutics for the treatment of diseases characterised by low bone mass [317].

Polo-like kinase (PLK) family

Enzymes → Kinases (EC 2.7.x.x) → Other protein kinases → Polo-like kinase (PLK) family

Nomenclature	polo-like kinase 4
Common abbreviation	PLK4
HGNC, UniProt	<i>PLK4</i> , O00444
EC number	2.7.11.21
Inhibitors	CFI-400945 (pIC ₅₀ 8.6) [320]

STE7 family

Enzymes → Kinases (EC 2.7.x.x) → STE: Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases → STE7 family

Nomenclature	mitogen-activated protein kinase kinase 1	mitogen-activated protein kinase kinase 2
Common abbreviation	MEK1	MEK2
HGNC, UniProt	<i>MAP2K1</i> , Q02750	<i>MAP2K2</i> , P36507
EC number	2.7.12.2	2.7.12.2
Inhibitors	trametinib (pIC ₅₀ 9–9.1) [173, 536], PD 0325901 (pIC ₅₀ 8.1) [195], binimetinib (pIC ₅₀ 7.9) [382], refametinib (pIC ₅₀ 7.7) [229], CI-1040 (pK _d 6.9) [105]	trametinib (pIC ₅₀ 8.7) [536], binimetinib (pIC ₅₀ 7.9) [382], refametinib (pIC ₅₀ 7.3) [229]

Abl family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Abl family

Nomenclature	ABL proto-oncogene 1, non-receptor tyrosine kinase
Common abbreviation	Abl
HGNC, UniProt	ABL1, P00519
EC number	2.7.10.2
Inhibitors	compound 8h (pIC ₅₀ 9.7) [487], dasatinib (pIC ₅₀ 9.6) [258], compound 24 (pIC ₅₀ 9.3) [110], PD-173955 (pK _d 9.2) [105], bosutinib (pIC ₅₀ 9) [176], PD-173955 (pIC ₅₀ ~8.3) [346], bafetinib (pIC ₅₀ 7.6–8.2) [216, 257], ponatinib (pIC ₅₀ 8.1) [220], nilotinib (pIC ₅₀ 7.8) [356], PP121 (pIC ₅₀ 7.7) [14], imatinib (pIC ₅₀ 6.7) [216], GNF-5 (pIC ₅₀ 6.7) [549]

Ack family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Ack family

Nomenclature	tyrosine kinase, non-receptor, 2
Common abbreviation	Ack
HGNC, UniProt	TNK2, Q07912
EC number	2.7.10.2
Inhibitors	compound 30 (pIC ₅₀ 9) [114]

Janus kinase (JakA) family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Janus kinase (JakA) family

Nomenclature	Janus kinase 1	Janus kinase 2	Janus kinase 3	tyrosine kinase 2
Common abbreviation	JAK1	JAK2	JAK3	Tyk2
HGNC, UniProt	JAK1 , P23458	JAK2 , O60674	JAK3 , P52333	TYK2 , P29597
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	ruxolitinib (pIC ₅₀ 8.5–10.1) [191 , 395], filgotinib (pIC ₅₀ 8) [497]	NS-018 (pIC ₅₀ 9.1) [350], BMS-911543 (pIC ₅₀ 9) [393], AT-9283 (pIC ₅₀ 8.9) [218], XL019 (pIC ₅₀ 8.7) [143], fedratinib (pIC ₅₀ 8.5) [311 , 521], gandotinib (pIC ₅₀ 8.4) [308]	AT-9283 (pIC ₅₀ 9) [218]	–
Selective inhibitors	–	compound 1d (pIC ₅₀ >9) [509]	–	–
Comments	–	The JAK2 ^{V617F} mutation, which causes constitutive activation, plays an oncogenic role in the pathogenesis of the myeloproliferative disorders, polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis [58 , 109]. Small molecule compounds which inhibit aberrant JAK2 activity are being developed as novel anti-cancer pharmaceuticals.	–	–

Src family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Src family

Nomenclature	BLK proto-oncogene, Src family tyrosine kinase	fyn-related Src family tyrosine kinase	FYN proto-oncogene, Src family tyrosine kinase	LYN proto-oncogene, Src family tyrosine kinase	SRC proto-oncogene, non-receptor tyrosine kinase
Common abbreviation	Blk	FRK	Fyn	Lyn	Src
HGNC, UniProt	BLK , P51451	FRK , P42685	FYN , P06241	LYN , P07948	SRC , P12931
EC number	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2	2.7.10.2

(continued)					
Nomenclature	BLK proto-oncogene, Src family tyrosine kinase	fyn-related Src family tyrosine kinase	FYN proto-oncogene, Src family tyrosine kinase	LYN proto-oncogene, Src family tyrosine kinase	SRC proto-oncogene, non-receptor tyrosine kinase
Inhibitors	–	–	–	bafetinib (pIC ₅₀ 8) [216]	WH-4-023 (pIC ₅₀ 8.2) [318], PD166285 (pK _i 8.1) [371], PP121 (pIC ₅₀ 7.8) [14], ENMD-2076 (pIC ₅₀ 7.7) [389]

Tec family

Enzymes → Kinases (EC 2.7.x.x) → TK: Tyrosine kinase → Tec family

Nomenclature	BMX non-receptor tyrosine kinase	Bruton agammaglobulinemia tyrosine kinase	TXK tyrosine kinase
Common abbreviation	Etk	Btk	TXK
HGNC, UniProt	BMX, P51813	BTK, Q06187	TXK, P42681
EC number	2.7.10.2	2.7.10.2	2.7.10.2
Inhibitors	–	ibrutinib (pIC ₅₀ 9.3) [370], compound 31 [PMID: 24915291] (pIC ₅₀ 8.4) [285], compound 38 [PMID: 24915291] (pIC ₅₀ >8.4) [285]	–
Selective inhibitors	–	CGI1746 (pIC ₅₀ 8.7) [112]	–

RAF family

Enzymes → Kinases (EC 2.7.x.x) → TKL: Tyrosine kinase-like → RAF family

Nomenclature	B-Raf proto-oncogene, serine/threonine kinase	Raf-1 proto-oncogene, serine/threonine kinase
Common abbreviation	B-Raf	c-Raf
HGNC, UniProt	BRAF, P15056	RAF1, P04049
EC number	2.7.11.1	2.7.11.1

(continued)		
Nomenclature	B-Raf proto-oncogene, serine/threonine kinase	Raf-1 proto-oncogene, serine/threonine kinase
Inhibitors	GDC-0879 (pIC ₅₀ 9.7–9.9) [105 , 193], dabrafenib (pIC ₅₀ 8.5) [277], regorafenib (pIC ₅₀ 7.6) [545], vemurafenib (pIC ₅₀ 7) [510], PLX-4720 (pK _d 6.5) [105], compound 2 [PMID: 26061392] (pK _d 6.3) [215], CHIR-265 (pK _d 5.9) [105]	–
Selective inhibitors	–	GW5074 (pIC ₅₀ 8.1) [80]

Peptidases and proteinases

Enzymes → [Peptidases and proteinases](#)

Overview: Peptidases and proteinases hydrolyse peptide bonds, and can be simply divided on the basis of whether terminal peptide bonds are cleaved (exopeptidases and exoproteinases) at the amino terminus (aminopeptidases) or carboxy terminus (car-

boxypeptidases). Non-terminal peptide bonds are cleaved by endopeptidases and endoproteinases, which are divided into serine endopeptidases (EC 3.4.21.-), cysteine endopeptidases (EC 3.4.22.-), aspartate endopeptidases (EC 3.4.23.-), metalloendopeptidases

(EC 3.4.24.-) and threonine endopeptidases (EC 3.4.25.-). It is beyond the scope of the Guide to list all peptidase and proteinase activities; this summary focuses on selected enzymes of significant pharmacological interest.

A1: Pepsin

Enzymes → [Peptidases and proteinases](#) → [AA: Aspartic \(A\) Peptidases](#) → [A1: Pepsin](#)

Nomenclature	renin
HGNC, UniProt	REN , P00797
EC number	3.4.23.15
Inhibitors	aliskiren (pIC ₅₀ 9.2) [532]

A22: Presenilin

Enzymes → Peptidases and proteinases → AD: Aspartic (A) Peptidases → A22: Presenilin

Overview: Presenilin (PS)-1 or -2 act as the catalytic component/essential co-factor of the γ -secretase complex responsible for the final carboxy-terminal cleavage of amyloid precursor protein (APP) [249] in the generation of amyloid beta (A β) [6, 471]. Given that the accumulation and aggregation of A β in the brain is pivotal in the development of Alzheimer's disease (AD), inhibition

of PS activity is one mechanism being investigated as a therapeutic option for AD [177]. Several small molecule inhibitors of PS-1 have been investigated, with some reaching early clinical trials, but none have been formally approved. Dewji *et al* (2015) have reported that small peptide fragments of human PS-1 can significantly inhibit A β production (total A β , A β 40 and A β 42)

both *in vitro* and when infused in to the brains of APP transgenic mice [111]. The most active small peptides in this report were P4 [PMID: 25923432] and P8 [PMID: 25923432], from the amino-terminal domain of PS-1.

C14: Caspase

Enzymes → Peptidases and proteinases → CD: Cysteine (C) Peptidases → C14: Caspase

Overview: Caspases, (E.C. 3.4.22.-) which derive their name from Cysteine ASpartate-specific proteASES, include at least two families; initiator caspases (caspases 2, 8, 9 and 10), which are able to hydrolyse and activate a second family of effector caspases (cas-

pases 3, 6 and 7), which themselves are able to hydrolyse further cellular proteins to bring about programmed cell death. Caspases are heterotetrameric, being made up of two pairs of subunits, generated by a single gene product, which is proteolysed to form the

mature protein. Members of the mammalian inhibitors of apoptosis proteins (IAP) are able to bind the procaspases, thereby preventing maturation to active proteinases.

Comments: CARD16 (Caspase recruitment domain-containing protein 16, caspase-1 inhibitor COP, CARD only domain-containing protein 1, pseudo interleukin-1 β converting enzyme, pseudo-ICE, ENSG00000204397) shares sequence similarity with some of the caspases.

M1: Aminopeptidase N

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M1: Aminopeptidase N

Overview: Aminopeptidases catalyze the cleavage of amino acids from the amino (N) terminus of protein or peptide substrates, and are involved in many essential cellular functions. Members of this enzyme family may be monomeric or multi-subunit complexes, and many are zinc metalloenzymes [480].

M2: Angiotensin-converting (ACE and ACE2)

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M2: Angiotensin-converting (ACE and ACE2)

Nomenclature	Angiotensin-converting enzyme
Common abbreviation	ACE
HGNC, UniProt	ACE, P12821
EC number	3.4.15.1
Endogenous substrates	angiotensin I (AGT, P01019) > angiotensin II (AGT, P01019)
Inhibitors	zofenoprilat (pK _i 9.4) [270] – Rabbit, captopril (pK _i 8.4) [331], zofenopril
Selective inhibitors	perindoprilat (pIC ₅₀ 9) [67], cilazaprilat (pIC ₅₀ 8.7) [514] – Rabbit, imidaprilat (pIC ₅₀ 8.7) [409], lisinopril-tryptophan (C-domain assay) (pIC ₅₀ 8.2) [515], RXP-407 (N-domain selective inhibition) (pIC ₅₀ 8.1) [434], fosinoprilat (pIC ₅₀ 8) [106] – Rabbit, enalaprilat (pIC ₅₀ 7.5) [79], benazeprilat (pIC ₅₀ 6.6) [282]
Comments	Reports of ACE GPI hydrolase activity [265] have been refuted [283]

M10: Matrix metalloproteinase

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M10: Matrix metalloproteinase

Overview: Matrix metalloproteinases (MMP) are calcium- and zinc-dependent proteinases regulating the extracellular matrix and are often divided (*e.g.* [501]) on functional and structural bases into gelatinases, collagenases, stromelysinases and matrilysins, as well as membrane type-MMP (MT-MMP).

Nomenclature	MMP2	MMP8
HGNC, UniProt	MMP2, P08253	MMP8, P22894
EC number	3.4.24.24	3.4.24.34
Selective inhibitors	ARP100 [493]	–

Comments: A number of small molecule ‘broad spectrum’ inhibitors of MMP have been described, including marimastat and batimastat.

Tissue inhibitors of metalloproteinase (TIMP) proteins are endogenous inhibitors acting to chelate MMP proteins: TIMP1 (TIMP1, P01033), TIMP2 (TIMP2, P16035), TIMP3 (TIMP3, P35625), TIMP4 (TIMP4, Q99727)

M12: Astacin/Adamalysin

Enzymes → Peptidases and proteinases → MA: Metallo (M) Peptidases → M12: Astacin/Adamalysin

Overview: ADAM (A Disintegrin And Metalloproteinase domain containing proteins) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

ADAMTS (with thrombospondin motifs) metalloproteinases cleave cell-surface or transmembrane proteins to generate soluble and membrane-limited products.

Comments: Additional ADAM family members include AC123767.2 (cDNA FLJ58962, moderately similar to mouse ADAM3, ENSG00000231168), AL160191.3 (ADAM21-like protein, [ENSG00000235812](#)), AC136428.3-2 (ENSG00000185520) and ADAMDEC1 (decysin 1, [ENSG00000134028](#)).

Other ADAMTS family members include AC104758.12-5 (FLJ00317 protein Fragment ENSG00000231463), AC139425.3-1 (ENSG00000225577), and AC126339.6-1 (ENSG00000225734).

M28: Aminopeptidase Y

Enzymes → Peptidases and proteinases → MH: Metallo (M) Peptidases → M28: Aminopeptidase Y

Nomenclature	Folate hydrolase (prostate-specific membrane antigen) 1
HGNC, UniProt	FOLH1 , Q04609
EC number	3.4.17.21
Antibodies	capromab (Binding)

Comment: folate hydrolase is also known as NAALADase as it is responsible for the hydrolysis of N-acetylaspartylglutamate to form N-acetylaspartate and L-glutamate. In the gut, the enzyme assists in the assimilation of folate by hydrolysing dietary poly-gamma-glutamylfolate. The enzyme is highly expressed in the prostate, and its expression is up-regulated in cancerous tissue. A tagged version of the antibody capromab has been used for imaging purposes.

M19: Membrane dipeptidase

Enzymes → Peptidases and proteinases → MJ: Metallo (M) Peptidases → M19: Membrane dipeptidase

Nomenclature	Dipeptidase 1
HGNC, UniProt	<i>DPEP1</i> , P16444
EC number	3.4.13.19: LTD ₄ + H ₂ O = LTE ₄ + glycine
Inhibitors	cilastatin (p <i>K</i> _i 6) [179] – Unknown

S1: Chymotrypsin

Enzymes → Peptidases and proteinases → PA: Serine (S) Peptidases → S1: Chymotrypsin

Nomenclature	complement component 1, r subcomponent	coagulation factor II (thrombin)	coagulation factor X	elastase, neutrophil expressed
HGNC, UniProt	<i>C1R</i> , P00736	<i>F2</i> , P00734	<i>F10</i> , P00742	<i>ELANE</i> , P08246
EC number	3.4.21.41	3.4.21.5	3.4.21.6	3.4.21.37
Inhibitors	nafamostat (pIC ₅₀ 4.9) [203]	lepirudin (p <i>K</i> _i 13) [511], desirudin (p <i>K</i> _i 12.7) [242], AZ12971554 (p <i>K</i> _i 9.5) [16], melagatran (p <i>K</i> _i 8.7) [186], bivalirudin (p <i>K</i> _i 8.6) [527], dabigatran (p <i>K</i> _i 8.3) [198], argatroban (p <i>K</i> _i 7.7) [225]	rivaroxaban (p <i>K</i> _i 9.4) [380], edoxaban (p <i>K</i> _i 9.2) [385], apixaban (p <i>K</i> _i 9.1) [528]	alvelestat (p <i>K</i> _i 8) [463], sivelestat (pIC ₅₀ 7.4) [96]
Selective inhibitors	–	AR-H067637 (pIC ₅₀ 8.4) [108]	–	–

Nomenclature	plasminogen	plasminogen activator, tissue	protease, serine, 1 (trypsin 1)	tryptase alpha/beta 1
HGNC, UniProt	<i>PLG</i> , P00747	<i>PLAT</i> , P00750	<i>PRSS1</i> , P07477	<i>TPSAB1</i> , Q15661
EC number	3.4.21.7	3.4.21.68	3.4.21.4	3.4.21.59
Inhibitors	aprotinin {Bovine} (Binding) (pIC ₅₀ 6.8) [454], tranexamic acid (Binding) (pIC ₅₀ 3.6) [454], 6-aminocaproic acid (Binding)	6-aminocaproic acid	nafamostat (pIC ₅₀ 7.8) [203]	nafamostat (pIC ₅₀ 10) [342]
Selective inhibitors	–	–	–	gabexate (pIC ₅₀ 8.5) [127]

T1: Proteasome

Enzymes → Peptidases and proteinases → PB: Threonine (T) Peptidases → T1: Proteasome

Overview: The T1 macropain beta subunits form the catalytic proteinase core of the 20S proteasome complex [86]. This catalytic core enables the degradation of peptides with Arg, Phe, Tyr, Leu, and Glu adjacent to the cleavage site. The β5 subunit is the principal target of the approved drug proteasome inhibitor **bortezomib**.

Nomenclature	proteasome (prosome, macropain) subunit, beta type, 5
HGNC, UniProt	<i>PSMB5</i> , P28074
EC number	3.4.25.1
Inhibitors	bortezomib (pIC ₅₀ 7.7) [347]
Selective inhibitors	ixazomib (pK _i 9) [273]

S8: Subtilisin

Enzymes → Peptidases and proteinases → SB: Serine (S) Peptidases → S8: Subtilisin

Overview: One member of this family has garnered intense interest as a clinical drug target. As liver PCSK9 acts to maintain cholesterol homeostasis, it has become a target of intense interest for clinical drug development. Inhibition of PCSK9 can lower low-density cholesterol (LDL-C) by clearing LDLR-bound

LDL particles, thereby lowering circulating cholesterol levels. It is hypothesised that this action may improve outcomes in patients with atherosclerotic cardiovascular disease [297, 416, 462]. Therapeutics which inhibit PCSK9 are viewed as potentially lucrative replacements for statins, upon statin patent expiry. Sev-

eral monoclonal antibodies including [alirocumab](#), [evolocumab](#), [bococizumab](#), RG-7652 and LY3015014 are under development. One RNAi therapeutic, code named ALN-PCS02, is also in development [99, 139, 146].

S9: Prolyl oligopeptidase

Enzymes → Peptidases and proteinases → SC: Serine (S) Peptidases → S9: Prolyl oligopeptidase

Nomenclature	dipeptidyl-peptidase 4
HGNC, UniProt	DPP4 , P27487
EC number	3.4.14.5
Endogenous substrates	glucagon-like peptide 1 (GCG , P01275)
Inhibitors	saxagliptin (p <i>K</i> _i 9.2) [184], linagliptin (p <i>K</i> _i 9) [122], sitagliptin (p <i>K</i> _i 8.1) [104], vildagliptin (p <i>K</i> _i 7.8) [184]

Acetylcholine turnover

Enzymes → Acetylcholine turnover

Overview: Acetylcholine is familiar as a neurotransmitter in the central nervous system and in the periphery. In the somatic nervous system, it activates [nicotinic acetylcholine receptors](#) at the skeletal neuromuscular junction. It is also employed in the autonomic nervous system, in both parasympathetic and sympathetic branches; in the former, at the smooth muscle neuromuscu-

lar junction, activating [muscarinic acetylcholine receptors](#). In the latter, acetylcholine is involved as a neurotransmitter at the ganglion, activating nicotinic acetylcholine receptors. Acetylcholine is synthesised in neurones through the action of choline O-acetyltransferase and metabolised after release through the extracellular action of acetylcholinesterase and cholinesterase. Choline

is accumulated from the extracellular medium by selective transporters (see [SLC5A7](#) and the [SLC44](#) family). Acetylcholine is accumulated in synaptic vesicles through the action of the vesicular acetylcholine transporter [SLC18A3](#).

Nomenclature	choline O-acetyltransferase	acetylcholinesterase (Yt blood group)	butyrylcholinesterase
Common abbreviation	ChAT	AChE	BChE
HGNC, UniProt	CHAT , P28329	ACHE , P22303	BCHE , P06276
EC number	2.3.1.6 : acetyl CoA + choline = acetylcholine + coenzyme A	3.1.1.7 : acetylcholine + H ₂ O = acetic acid + choline + H ⁺	3.1.1.7 : acetylcholine + H ₂ O = acetic acid + choline + H ⁺
Inhibitors	–	tacrine (pK _i 7.5) [52], galantamine (pIC ₅₀ 6.3) [87], rivastigmine (pIC ₅₀ 5.4) [305]	rivastigmine (pIC ₅₀ 7.4) [305], tacrine (pK _i 7.2) [52]
(Sub)family-selective inhibitors	–	physostigmine (pIC ₅₀ 7.6–7.8) [305]	physostigmine (pIC ₅₀ 7.6–7.8) [305]
Selective inhibitors	–	donepezil (pIC ₅₀ 7.7–8.3) [62 , 160 , 305], BW284C51 (pIC ₅₀ 7.7) [172]	bambuterol (pIC ₅₀ 8.5) [172]
Comments	Splice variants of choline O-acetyltransferase are suggested to be differentially distributed in the periphery and CNS (see [28]).	–	–

Comments: A number of organophosphorus compounds inhibit acetylcholinesterase and cholinesterase irreversibly, including pesticides such as chlorpyrifos-oxon, and nerve agents such as tabun, soman and sarin. AChE is unusual in its exceptionally high turnover rate which has been calculated at 740 000/min/molecule [[505](#)].

Further Reading

- Abreu-Villaça Y *et al.* (2011) Developmental aspects of the cholinergic system. *Behav. Brain Res.* **221**: 367-78 [[PMID:20060019](#)]
- Bellier JP *et al.* (2011) Peripheral type of choline acetyltransferase: biological and evolutionary implications for novel mechanisms in cholinergic system. *J. Chem. Neuroanat.* **42**: 225-35 [[PMID:21382474](#)]
- Engel AG *et al.* (2015) Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment.

- Lancet Neurol* **14**: 420-34 [[PMID:25792100](#)]
- Rosini M *et al.* (2014) Multi-target design strategies in the context of Alzheimer's disease: acetylcholinesterase inhibition and NMDA receptor antagonism as the driving forces. *Neurochem. Res.* **39**: 1914-23 [[PMID:24493627](#)]
- Zimmermann M. (2013) Neuronal AChE splice variants and their non-hydrolytic functions: redefining a target of AChE inhibitors? *Br. J. Pharmacol.* **170**: 953-67 [[PMID:23991627](#)]

Adenosine turnover

Enzymes → Adenosine turnover

Overview: A multifunctional, ubiquitous molecule, **adenosine** acts at cell-surface G protein-coupled receptors, as well as numerous enzymes, including protein kinases and adenylyl cyclase. Extracellular adenosine is thought to be produced either by export or

by metabolism, predominantly through ecto-5'-nucleotidase activity (also producing inorganic phosphate). It is inactivated either by extracellular metabolism *via* adenosine deaminase (also producing ammonia) or, following uptake by nucleoside trans-

porters, *via* adenosine deaminase or adenosine kinase (requiring **ATP** as co-substrate). Intracellular adenosine may be produced by cytosolic 5'-nucleotidases or through S-adenosylhomocysteine hydrolase (also producing **L-homocysteine**).

Nomenclature	Adenosine deaminase	Adenosine kinase	Ecto-5'-Nucleotidase	S-Adenosylhomocysteine hydrolase
Common abbreviation	ADA	ADK	NT5E	SAHH
HGNC, UniProt	ADA , P00813	ADK , P55263	NT5E , P21589	AHCY , P23526
EC number	3.5.4.4: adenosine + H ₂ O = inosine + NH ₃	2.7.1.20	3.1.3.5	3.3.1.1
Endogenous substrates	–	–	–	S-adenosylhomocysteine
Rank order of affinity	2'-deoxyadenosine > adenosine	adenosine	adenosine 5'-monophosphate, 5'-GMP, 5'-inosine monophosphate, 5'-UMP > 5'-dAMP, 5'-dGMP	–
Products	2'-deoxyinosine, inosine	adenosine 5'-monophosphate	uridine, inosine, guanine, adenosine	adenosine
Inhibitors	–	–	–	DZNep (pK _i 12.3) [174] – Hamster
Selective inhibitors	pentostatin (pIC ₅₀ 10.8) [3], EHNA (pK _i 8.8) [3]	A134974 (pIC ₅₀ 10.2) [325], ABT702 (pIC ₅₀ 8.8) [236]	αβ-methyleneADP (pIC ₅₀ 8.7) [50]	3-deazaadenosine (pIC ₅₀ 8.5) [185]

Comments: An extracellular adenosine deaminase activity, termed ADA2 or adenosine deaminase growth factor (ADGF, [CECRI](#), [Q9NZKS](#)) has been identified [[94](#), [309](#)], which is insensitive to [EHNA](#) [[546](#)]. Other forms of adenosine deaminase act on ribonucleic acids and may be divided into two families: [ADATI](#) ([Q9BUB4](#)) deaminates transfer RNA; [ADAR](#) (EC 3.5.4.37, also

known as 136 kDa double-stranded RNA-binding protein, P136, K88DSRBP, Interferon-inducible protein 4); [ADARBI](#) (EC 3.5.-.-, , also known as dsRNA adenosine deaminase) and [ADARB2](#) (EC 3.5.-.-, , also known as dsRNA adenosine deaminase B2, RNA-dependent adenosine deaminase 3) act on double-stranded RNA. Particular polymorphisms of the ADA gene result in loss-of-function and se-

vere combined immunodeficiency syndrome. Adenosine deaminase is able to complex with dipeptidyl peptidase IV (EC 3.4.14.5, [DPP4](#), also known as T-cell activation antigen CD26, TP103, adenosine deaminase complexing protein 2) to form a cell-surface activity [[248](#)].

Further Reading

Antonioni L *et al.* (2013) CD39 and CD73 in immunity and inflammation. *Trends Mol Med* **19**: 355-67

[PMID:23601906]

Boison D. (2013) Adenosine kinase: exploitation for therapeutic gain. *Pharmacol. Rev.* **65**: 906-43

[PMID:23592612]

Cortés A *et al.* (2015) Moonlighting adenosine deaminase: a target protein for drug development.

Med Res Rev **35**: 85-125 [PMID:24933472]

Tomaselli S *et al.* (2014) The RNA editing enzymes ADARs: mechanism of action and human disease.

Cell Tissue Res. **356**: 527-32 [PMID:24770896]

Zimmermann H *et al.* (2012) Cellular function and molecular structure of ecto-nucleotidases. *Purinergic Signal.* **8**: 437-502 [PMID:22555564]

Amino acid hydroxylases

Enzymes → Amino acid hydroxylases

Overview: The amino acid hydroxylases (monooxygenases), EC.1.14.16.-, are iron-containing enzymes which utilise molecular oxygen and [sapropterin](#) as co-substrate and co-factor, respectively. In humans, as well as in other mammals, there are two distinct L-Tryptophan hydroxylase 2 genes. In humans, these genes are located on chromosomes 11 and 12 and encode two different homologous enzymes, TPH1 and TPH2.

Nomenclature	L-Phenylalanine hydroxylase	L-Tyrosine hydroxylase	L-Tryptophan hydroxylase 1	L-Tryptophan hydroxylase 2
HGNC, UniProt	PAH , P00439	TH , P07101	TPH1 , P17752	TPH2 , Q8IWU9
EC number	1.14.16.1: L-phenylalanine + O ₂ -> L-tyrosine	1.14.16.2: L-tyrosine + O ₂ -> levodopa	1.14.16.4	1.14.16.4
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [1]	Protein kinase A-mediated phosphorylation [239]	Protein kinase A-mediated phosphorylation [240]	Protein kinase A-mediated phosphorylation [240]
Endogenous substrates	L-phenylalanine	L-tyrosine	L-tryptophan	L-tryptophan
Products	L-tyrosine	levodopa	5-hydroxy-L-tryptophan	5-hydroxy-L-tryptophan
Cofactors	sapropterin	sapropterin, Fe ²⁺	–	–
Selective activators	sapropterin (pK _i 5.4) [481]	–	–	–
Inhibitors	–	methyltyrosine	–	–
Selective inhibitors	α-methylphenylalanine [180] – Rat, fenclonine	α-propyldopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	α-propyldopacetamide, 6-fluorotryptophan [352], fenclonine, fenfluramine	α-propyldopacetamide, 6-fluorotryptophan [352], fenclonine, fenfluramine
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monoxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [102].	–	–

Further Reading

- Amireault P *et al.* (2013) Life without peripheral serotonin: insights from tryptophan hydroxylase 1 knockout mice reveal the existence of paracrine/autocrine serotonergic networks. *ACS Chem Neurosci* **4**: 64-71 [PMID:23336045]
- Daubner SC *et al.* (2011) Tyrosine hydroxylase and regulation of dopamine synthesis. *Arch. Biochem. Biophys.* **508**: 1-12 [PMID:21176768]
- Flydal MI *et al.* (2013) Phenylalanine hydroxylase: function, structure, and regulation. *IUBMB Life* **65**: 341-9 [PMID:23457044]
- Roberts KM *et al.* (2013) Mechanisms of tryptophan and tyrosine hydroxylase. *IUBMB Life* **65**: 350-7 [PMID:23441081]
- Tekin I *et al.* (2014) Complex molecular regulation of tyrosine hydroxylase. *J Neural Transm* **121**: 1451-81 [PMID:24866693]

L-Arginine turnover

Enzymes → L-Arginine turnover

Overview: L-arginine is a basic amino acid with a guanidino sidechain. As an amino acid, metabolism of L-arginine to form L-ornithine, catalysed by arginase, forms the last step of the urea production cycle. L-Ornithine may be utilised as a precursor of polyamines (see [Carboxylases and Decarboxylases](#)) or recycled via L-argininosuccinic acid to L-arginine. L-Arginine may itself be decarboxylated to form agmatine, although the

prominence of this pathway in human tissues is uncertain. L-Arginine may be used as a precursor for guanidoacetic acid formation in the creatine synthesis pathway under the influence of arginine:glycine amidinotransferase with L-ornithine as a byproduct. Nitric oxide synthase uses L-arginine to generate nitric oxide, with L-citrulline also as a byproduct. L-Arginine in proteins may be subject to post-translational mod-

ification through methylation, catalysed by protein arginine methyltransferases. Subsequent proteolysis can liberate asymmetric N^G,N^G-dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of nitric oxide synthase activities. ADMA is hydrolysed by dimethylarginine dimethylhydrolase activities to generate L-citrulline and dimethylamine.

Further Reading

- Moncada S *et al.* (1997) International Union of Pharmacology Nomenclature in Nitric Oxide Research. *Pharmacol. Rev.* **49**: 137-42 [PMID:9228663]
- Tang L *et al.* (2014) Targeting NOS as a therapeutic approach for heart failure. *Pharmacol. Ther.* **142**: 306-15 [PMID:24380841]
- Tratsiakovich Y *et al.* (2013) Arginase as a target for treatment of myocardial ischemia-reperfusion injury. *Eur. J. Pharmacol.* **720**: 121-3 [PMID:24183975]
- Whiteley CG. (2014) Arginine metabolising enzymes as targets against Alzheimers' disease. *Neurochem. Int.* **67**: 23-31 [PMID:24508404]
- Yang Y *et al.* (2013) Protein arginine methyltransferases and cancer. *Nat. Rev. Cancer* **13**: 37-50 [PMID:23235912]

Arginase

Enzymes → L-Arginine turnover → Arginase

Overview: Arginase (EC 3.5.3.1) are manganese-containing isoforms, which appear to show differential distribution, where the ARG1 isoform predominates in the liver and erythrocytes, while ARG2 is associated more with the kidney.

Comments: N^{ω} -hydroxyarginine, an intermediate in NOS metabolism of L-arginine acts as a weak inhibitor and may function as a physiological regulator of arginase activity. Although isoform-selective inhibitors of arginase are not available, examples of inhibitors selective for arginase compared to NOS are N^{ω} -hydroxy-nor-L-arginine [483], S-(2-boronoethyl)-L-cysteine [90, 256] and 2(S)-amino-6-boronoheptanoic acid [22, 90].

Arginine:glycine amidinotransferase

Enzymes → L-Arginine turnover → Arginine:glycine amidinotransferase

Nomenclature	Arginine:glycine amidinotransferase
Common abbreviation	AGAT
HGNC, UniProt	<i>GATM</i> , P50440
EC number	2.1.4.1

Dimethylarginine dimethylaminohydrolases

Enzymes → L-Arginine turnover → Dimethylarginine dimethylaminohydrolases

Overview: Dimethylarginine dimethylaminohydrolases (DDAH, EC 3.5.3.18) are cytoplasmic enzymes which hydrolyse N^G, N^G -dimethyl-L-arginine to form dimethylamine and L-citrulline.

Nomenclature	N^G, N^G -Dimethylarginine dimethylaminohydrolase 1	N^G, N^G -Dimethylarginine dimethylaminohydrolase 2
Common abbreviation	DDAH1	DDAH2
HGNC, UniProt	<i>DDAH1</i> , O94760	<i>DDAH2</i> , O95865
EC number	3.5.3.18	3.5.3.18
Cofactors	Zn ²⁺	–

Nitric oxide synthases

Enzymes → L-Arginine turnover → Nitric oxide synthases

Overview: Nitric oxide synthases (NOS, [E.C. 1.14.13.39](#)) utilise [L-arginine](#) (not D-arginine) and molecular oxygen to generate nitric oxide and [L-citrulline](#). The nomenclature suggested by **NC-IUPHAR** of NOS I, II and III [[340](#)] has not gained wide accep-

tance. eNOS and nNOS isoforms are activated at concentrations of calcium greater than 100 nM, while iNOS shows higher affinity for Ca^{2+} /[calmodulin](#) ([CALM1 CALM2 CALM3](#), [P62158](#)) and thus appears to be constitutively active. All the three isoforms are ho-

modimers and require [sapropterin](#), [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
Common abbreviation	eNOS	iNOS	nNOS
HGNC, UniProt	NOS3 , P29474	NOS2 , P35228	NOS1 , P29475
EC number	1.14.13.39	1.14.13.39	1.14.13.39
Inhibitors	–	–	N^ωpropyl-L-arginine (pK_i 7.2) [548] – Rat
Selective inhibitors	–	1400W (pIC_{50} 8.2) [168], 2-amino-4-methylpyridine (pIC_{50} 7.4) [131], PIBTU (pIC_{50} 7.3) [169], NIL (pIC_{50} 5.5) [341], aminoguanidine [92]	3-bromo-7NI (pIC_{50} 6.1–6.5) [40], 7NI (pIC_{50} 5.3) [19]

Comments: The reductase domain of NOS catalyses the reduction of cytochrome c and other redox-active dyes [[322](#)]. $\text{NADPH}:\text{O}_2$ oxidoreductase catalyses the formation of superoxide anion/ H_2O_2 in the absence of [L-arginine](#) and [sapropterin](#).

Carboxylases and decarboxylases

Enzymes → Carboxylases and decarboxylases

Carboxylases

Enzymes → Carboxylases and decarboxylases → Carboxylases

Overview: The carboxylases allow the production of new carbon-carbon bonds by introducing HCO_3^- or CO_2 into target molecules. Two groups of carboxylase activities, some of which are bidirectional, can be defined on the basis of the cofactor requirement, making use of **biotin** (EC 6.4.1.-) or **vitamin K hydroquinone** (EC 4.1.1.-).

Nomenclature	Pyruvate carboxylase	Acetyl-CoA carboxylase 1	Acetyl-CoA carboxylase 2
Common abbreviation	PC	ACC1	ACC2
HGNC, UniProt	PC , P11498	ACACA , Q13085	ACACB , O00763
EC number	6.4.1.1	6.4.1.2	6.4.1.2
Endogenous substrates	ATP, pyruvic acid	ATP, acetyl CoA	acetyl CoA, ATP
Products	P_i , adenosine diphosphate, oxalacetic acid	P_i , adenosine diphosphate, malonyl-CoA	P_i , adenosine diphosphate, malonyl-CoA
Cofactors	biotin	biotin	biotin
Selective inhibitors	–	TOFA [294]	TOFA [294]
Comments	–	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.	Citrate and other dicarboxylic acids are allosteric activators of acetyl-CoA carboxylase.

Nomenclature	Propionyl-CoA carboxylase	γ -Glutamyl carboxylase
Common abbreviation	PCCA, PCCB	GGCX
HGNC, UniProt	PCCA , P05165 PCCB , P05166	GGCX , P38435
Subunits	Propionyl-CoA carboxylase α subunit Propionyl-CoA carboxylase β subunit	–
EC number	6.4.1.3	4.1.1.90
Endogenous substrates	propionyl-CoA, ATP	glutamyl peptides
Products	adenosine diphosphate, methylmalonyl-CoA, P_i	carboxyglutamyl peptides
Cofactors	biotin	vitamin K hydroquinone, NADPH

(continued)		
Nomenclature	Propionyl-CoA carboxylase	γ-Glutamyl carboxylase
Inhibitors	–	anisindione
Comments	Propionyl-CoA carboxylase is able to function in both forward and reverse activity modes, as a ligase (carboxylase) or lyase (decarboxylase), respectively.	Loss-of-function mutations in γ -glutamyl carboxylase are associated with clotting disorders .

Comments: Dicarboxylic acids including [citric acid](#) are able to activate ACC1/ACC2 activity allosterically. PCC is able to function in forward and reverse modes as a ligase (carboxylase) or lyase (decarboxylase) activity, respectively. Loss-of-function mutations in GGCX are associated with clotting disorders.

Decarboxylases

Enzymes → [Carboxylases and decarboxylases](#) → [Decarboxylases](#)

Overview: The decarboxylases generate CO₂ and the indicated products from acidic substrates, requiring [pyridoxal phosphate](#) or [pyruvic acid](#) as a co-factor.

Nomenclature	S-Adenosylmethionine decarboxylase	L-Arginine decarboxylase	L-Aromatic amino-acid decarboxylase	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
Common abbreviation	SAMDC	ADC	AADC	GAD1	GAD2
HGNC, UniProt	AMD1, P17707	AZIN2, Q96A70	DDC, P20711	GAD1, Q99259	GAD2, Q05329
EC number	4.1.1.50	4.1.1.19	4.1.1.28: levodopa -> dopamine + CO₂ 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO₂ This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO₂	4.1.1.15: L-glutamic acid + H⁺ -> GABA + CO₂	4.1.1.15: L-glutamic acid + H⁺ -> GABA + CO₂
Substrates	–	–	Deuterium-substituted L-DOPA [312]	–	–
Endogenous substrates	S-adenosyl methionine	L-arginine	levodopa, 5-hydroxy-L-tryptophan, L-tryptophan	L-glutamic acid, L-aspartic acid	L-glutamic acid, L-aspartic acid

(continued)					
Nomenclature	S-Adenosylmethionine decarboxylase	L-Arginine decarboxylase	L-Aromatic amino-acid	Glutamic acid decarboxylase 1	Glutamic acid decarboxylase 2
Products	S-adenosyl-L-methioninamine	agmatine [552]	5-hydroxytryptamine, dopamine	GABA	GABA
Cofactors	pyruvic acid	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate
Selective inhibitors	sardomozide (pIC ₅₀ 8) [455]	–	3-hydroxybenzylhydrazine, L-α-methyldopa, benserazide [101], carbidopa	s-allylglycine	s-allylglycine
Comments	s-allylglycine is also an inhibitor of SAMDC [368].	The presence of a functional ADC activity in human tissues has been questioned [89].	AADC is a homodimer.	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β -alanine [530]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β -alanine [530]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).

Nomenclature	Histidine decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase
Common abbreviation	HDC	MLYCD	ODC	PSDC
HGNC, UniProt	HDC , P19113	MLYCD , O95822	ODC1 , P11926	PISD , Q9UG56
EC number	4.1.1.22	4.1.1.9	4.1.1.17	4.1.1.65
Endogenous substrates	L-histidine	malonyl-CoA	L-ornithine	phosphatidylserine
Products	histamine	acetyl CoA	putrescine	phosphatidylethanolamine
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	pyruvic acid
Selective inhibitors	AMA , FMH [164]	–	APA (pIC ₅₀ 7.5) [456], eflornithine (pK _d 4.9) [394]	–

(continued)				
Nomenclature	Histidine decarboxylase	Malonyl-CoA decarboxylase	Ornithine decarboxylase	Phosphatidylserine decarboxylase
Comments	–	Inhibited by AMP-activated protein kinase-evoked phosphorylation [415]	The activity of ODC is regulated by the presence of an antizyme (ENSG00000104904) and an ODC antizyme inhibitor (ENSG00000155096).	S-allylglycine is also an inhibitor of SAMDC [368].

Further Reading

- Bale S *et al.* (2010) Structural biology of S-adenosylmethionine decarboxylase. *Amino Acids* **38**: 451–60 [PMID:19997761]
- Jitrapakdee S *et al.* (2008) Structure, mechanism and regulation of pyruvate carboxylase. *Biochem. J.* **413**: 369–87 [PMID:18613815]
- Lietzan AD *et al.* (2014) Functionally diverse biotin-dependent enzymes with oxaloacetate decarboxylase activity. *Arch. Biochem. Biophys.* **544**: 75–86 [PMID:24184447]
- Moya-García AA *et al.* (2009) Structural features of mammalian histidine decarboxylase reveal the basis for specific inhibition. *Br. J. Pharmacol.* **157**: 4–13 [PMID:19413567]
- Tong L. (2013) Structure and function of biotin-dependent carboxylases. *Cell. Mol. Life Sci.* **70**: 863–91 [PMID:22869039]
- Vance JE *et al.* (2013) Formation and function of phosphatidylserine and phosphatidylethanolamine in mammalian cells. *Biochim. Biophys. Acta* **1831**: 543–54 [PMID:22960354]

Catecholamine turnover

Enzymes → [Catecholamine turnover](#)

Overview: Catecholamines are defined by the presence of two adjacent hydroxyls on a benzene ring with a sidechain containing an amine. The predominant catecholamines in mammalian biology are the neurotransmitter/hormones [dopamine](#), [\(-\)-noradrenaline](#) (norepinephrine) and [\(-\)-adrenaline](#) (epinephrine). These hormone/transmitters are synthesized by sequential metabolism from [L-phenylalanine](#) via [L-tyrosine](#). Hydroxylation of [L-tyrosine](#) generates [levodopa](#),

which is decarboxylated to form [dopamine](#). Hydroxylation of the ethylamine sidechain generates [\(-\)-noradrenaline](#) (norepinephrine), which can be methylated to form [\(-\)-adrenaline](#) (epinephrine). In particular neuronal and adrenal chromaffin cells, the catecholamines [dopamine](#), [\(-\)-noradrenaline](#) and [\(-\)-adrenaline](#) are accumulated into vesicles under the influence of the [vesicular monoamine transporters](#) (VMAT1/SLC18A1 and VMAT2/SLC18A2). After release into the synapse or the blood-

stream, catecholamines are accumulated through the action of cell-surface transporters, primarily the dopamine ([DAT/SLC6A3](#)) and norepinephrine transporter ([NET/SLC6A2](#)). The primary routes of metabolism of these catecholamines are oxidation via monoamine oxidase activities of methylation via catechol O-methyltransferase.

Nomenclature	L-Phenylalanine hydroxylase	Tyrosine aminotransferase	L-Aromatic amino-acid decarboxylase
Common abbreviation	–	TAT	AADC
HGNC, UniProt	PAH , P00439	TAT , P17735	DDC , P20711

(continued)			
Nomenclature	L-Phenylalanine hydroxylase	Tyrosine aminotransferase	L-Aromatic amino-acid decarboxylase
EC number	1.14.16.1: L-phenylalanine + O₂ -> L-tyrosine	2.6.1.5: L-tyrosine + α-ketoglutaric acid -> 4-hydroxyphenylpyruvic acid + L-glutamic acid	4.1.1.28: levodopa -> dopamine + CO₂ 5-hydroxy-L-tryptophan -> 5-hydroxytryptamine + CO₂ This enzyme also catalyses the following reaction:: L-tryptophan -> tryptamine + CO₂
Endogenous activators	Protein kinase A-mediated phosphorylation (Rat) [1]	–	–
Substrates	–	–	Deuterium-substituted L-DOPA [312]
Endogenous substrates	L-phenylalanine	–	levodopa , 5-hydroxy-L-tryptophan , L-tryptophan
Products	L-tyrosine	–	5-hydroxytryptamine , dopamine
Cofactors	sapropterin	pyridoxal phosphate	pyridoxal phosphate
Selective activators	sapropterin (pK _i 5.4) [481]	–	–
Selective inhibitors	α-methylphenylalanine [180] – Rat, fenclonine	–	3-hydroxybenzylhydrazine , L-α-methyldopa , benserazide [101] , carbidopa
Comments	PAH is an iron bound homodimer or -tetramer from the same structural family as tyrosine 3-monooxygenase and the tryptophan hydroxylases. Deficiency or loss-of-function of PAH is associated with phenylketonuria	Tyrosine may also be metabolized in the liver by tyrosine transaminase to generate 4-hydroxyphenylpyruvic acid , which can be further metabolized to homogentisic acid. TAT is a homodimer, where loss-of-function mutations are associated with type II tyrosinemia .	AADC is a homodimer.

Nomenclature	L-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	Phenylethanolamine N-methyltransferase
Common abbreviation	–	DBH	PNMT
HGNC, UniProt	TH , P07101	DBH , P09172	PNMT , P11086
EC number	1.14.16.2: L-tyrosine + O₂ -> levodopa	1.14.17.1: dopamine + O₂ = (-)-noradrenaline + H₂O	2.1.1.28: (-)-noradrenaline -> (-)-adrenaline
Endogenous activators	Protein kinase A-mediated phosphorylation [239]	–	–
Endogenous substrates	L-tyrosine	–	–
Products	levodopa	–	–
Cofactors	sapropterin , Fe²⁺	Cu²⁺ , L-ascorbic acid	S-adenosyl methionine

(continued)			
Nomenclature	L-Tyrosine hydroxylase	Dopamine beta-hydroxylase (dopamine beta-monoxygenase)	Phenylethanolamine N-methyltransferase
Inhibitors	methyltyrosine	nepicastat (pIC ₅₀ 8) [458]	LY134046 (pK _i 7.6) [154]
Selective inhibitors	α-propylidopacetamide, 3-chlorotyrosine, 3-iodotyrosine, alpha-methyltyrosine	–	–
Comments	TH is a homotetramer, which is inhibited by dopamine and other catecholamines in a physiological negative feedback pathway [102].	DBH is a homotetramer. A protein structurally-related to DBH (<i>MOXD1</i> , <i>Q6UVY6</i>) has been described and for which a function has yet to be identified [71].	–

Nomenclature	Monoamine oxidase A	Monoamine oxidase B	Catechol-O-methyltransferase
Common abbreviation	MAO-A	MAO-B	COMT
HGNC, UniProt	<i>MAOA</i> , P21397	<i>MAOB</i> , P27338	<i>COMT</i> , P21964
EC number	1.4.3.4 (-)-adrenaline -> 3,4-dihydroxymandelic acid + NH ₃ (-)-noradrenaline -> 3,4-dihydroxymandelic acid + NH ₃ tyramine -> 4-hydroxyphenyl acetaldehyde + NH ₃ dopamine -> 3,4-dihydroxyphenylacetaldehyde + NH ₃ 5-hydroxytryptamine -> 5-hydroxyindole acetaldehyde + NH ₃	1.4.3.4	2.1.1.6: S-adenosyl-L-methionine + a catechol = S-adenosyl-L-homocysteine + a guaiacol (-)-noradrenaline -> normetanephrine dopamine -> 3-methoxytyramine 3,4-dihydroxymandelic acid -> vanillylmandelic acid (-)-adrenaline -> metanephrine
Cofactors	flavin adenine dinucleotide	flavin adenine dinucleotide	S-adenosyl methionine
Inhibitors	moclobemide (pK _i 8.3) [234], phenelzine (Irreversible inhibition) (pK _i 7.3) [36], tranylcypromine (pIC ₅₀ 4.7) [538], selegiline (pK _i 4.2) [333], bexlofaxone [100], clorgiline, pirlindole [327]	rasagiline (pIC ₅₀ 7.8) [542], phenelzine (Irreversible inhibition) (pK _i 7.8) [36], lazabemide (pK _i 7.1) [188, 489], selegiline (pK _i 5.7–6) [113, 333], tranylcypromine (pIC ₅₀ 4.7) [538]	tolcapone (soluble enzyme) (pK _i 9.6) [299], tolcapone (membrane-bound enzyme) (pK _i 9.5) [299], entacapone (soluble enzyme) (pK _i 9.5) [299], entacapone (membrane-bound enzyme) (pK _i 8.7) [299]
Selective inhibitors	–	safinamide (pK _i 6.3) [35]	–
Comments	–	–	COMT appears to exist in both membrane-bound and soluble forms. COMT has also been described to methylate steroids, particularly hydroxysteroids

Further Reading

Al-Nuaimi SK *et al.* (2012) Monoamine oxidase inhibitors and neuroprotection: a review. *Am J Ther* **19**: 436-48 [PMID:22960850]
 Fitzpatrick PF. (2012) Allosteric regulation of phenylalanine hydroxylase. *Arch. Biochem. Biophys.* **519**: 194-201 [PMID:22005392]
 Flydal MI *et al.* (2013) Phenylalanine hydroxylase: function, structure, and regulation. *IUBMB Life*

65: 341-9 [PMID:23457044]
 Ma Z *et al.* (2013) Structure-based drug design of catechol-O-methyltransferase inhibitors for CNS disorders. *Br J Clin Pharmacol* [PMID:23713800]
 Shih JC *et al.* (2011) Transcriptional regulation and multiple functions of MAO genes. *J Neural Transm* **118**: 979-86 [PMID:21359973]

Ceramide turnover

Enzymes → Ceramide turnover

Overview: Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence, Serine palmitoyltransferase generates 3-ketosphinganine, which is reduced to sphinganine (dihydrosphingosine). N-Acylation allows the formation of dihydroceramides, which are subsequently re-

duced to form ceramides. Once synthesized, ceramides are trafficked from the ER to the Golgi bound to the ceramide transfer protein, CERT (COL4A3BP, Q9Y5P4). Ceramide can be metabolized via multiple routes, ensuring tight regulation of its cellular levels. Addition of phosphocholine generates sphingomyelin while carbohydrate is added to form glucosyl- or galactosylceramides.

Ceramidase re-forms sphingosine or sphinganine from ceramide or dihydroceramide. Phosphorylation of ceramide generates ceramide phosphate. The determination of accurate kinetic parameters for many of the enzymes in the sphingolipid metabolic pathway is complicated by the lipophilic nature of the substrates.

Serine palmitoyltransferase

Enzymes → Ceramide turnover → Serine palmitoyltransferase

Overview: The functional enzyme is a heterodimer of SPT1 (LCB1) with either SPT2 (LCB2) or SPT3 (LCB2B); the small subunits of SPT (ssSPTa or ssSPTb) bind to the heterodimer to enhance enzymatic activity. The complexes of SPT1/SPT2/ssSPTa and SPT1/SPT2/ssSPTb were most active with palmitoylCoA as substrate, with the latter complex also showing some activity with stearoylCoA [190]. Complexes involving SPT3 appeared more broad in substrate selectivity, with incorporation of myristoylCoA prominent for SPT1/SPT3/ssSPTa complexes, while SP1/SPT3/ssSPTb complexes had similar activity with C16, C18 and C20 acylCoAs [190].

Nomenclature	serine palmitoyltransferase, long chain base subunit 1	serine palmitoyltransferase, long chain base subunit 2	serine palmitoyltransferase, long chain base subunit 3	serine palmitoyltransferase, small subunit A	serine palmitoyltransferase, small subunit B
Common abbreviation	SPT1	SPT2	SPT3	SPTSSA	SPTSSB
HGNC, UniProt	SPTLC1, O15269	SPTLC2, O15270	SPTLC3, Q9NUV7	SPTSSA, Q969W0	SPTSSB, Q8NFR3

(continued)					
Nomenclature	serine palmitoyltransferase, long chain base subunit 1	serine palmitoyltransferase, long chain base subunit 2	serine palmitoyltransferase, long chain base subunit 3	serine palmitoyltransferase, small subunit A	serine palmitoyltransferase, small subunit B
EC number	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A + CO ₂	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A CO ₂ +	2.3.1.50: L-serine + palmitoyl-CoA -> 3-ketosphinganine + coenzyme A CO ₂ +	–	–
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	–	–
Selective inhibitors	myriocin [334]	myriocin [334]	myriocin [334]	–	–

Ceramide synthase

Enzymes → Ceramide turnover → Ceramide synthase

Overview: This family of enzymes, also known as sphingosine *N*-acyltransferase, is located in the ER facing the cytosol with an as-yet undefined topology and stoichiometry. Ceramide synthase *in vitro* is sensitive to inhibition by the fungal derived toxin, fumonisin B1.

Nomenclature	ceramide synthase 1	ceramide synthase 2	ceramide synthase 3
Common abbreviation	CERS1	CERS2	CERS3
HGNC, UniProt	CERS1 , P27544	CERS2 , Q96G23	CERS3 , Q8IU89
EC number	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24: acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A
Substrates	C18-CoA [499]	C24- and C26-CoA [278]	C26-CoA and longer [337, 396]

Nomenclature	ceramide synthase 4	ceramide synthase 5	ceramide synthase 6
Common abbreviation	CERS4	CERS5	CERS6
HGNC, UniProt	CERS4, Q9HA82	CERS5, Q8N5B7	CERS6, Q6ZMG9
EC number	2.3.1.24 : acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24 : acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A	2.3.1.24 : acylCoA + sphinganine -> dihydroceramide + coenzyme A sphingosine + acylCoA -> ceramide + coenzyme A
Substrates	C18-, C20- and C22-CoA [405]	C16-CoA [274 , 405]	C14- and C16-CoA [336]

Sphingolipid Δ^4 -desaturase

Enzymes → Ceramide turnover → Sphingolipid Δ^4 -desaturase

Overview: DEGS1 and DEGS2 are 4TM proteins.

Nomenclature	delta(4)-desaturase, sphingolipid 1	delta(4)-desaturase, sphingolipid 2
HGNC, UniProt	DEGS1, O15121	DEGS2, Q6QHC5
EC number	1.14.-.-	1.14.-.-
Cofactors	NAD	NAD
Comments	Myristoylation of DEGS1 enhances its activity and targets it to the mitochondria [26].	–

Comments: DEGS1 activity is inhibited by a number of natural products, including [curcumin](#) and [\$\Delta^9\$ -tetrahydrocannabinol](#) [[130](#)].

Sphingomyelin synthase

Enzymes → Ceramide turnover → Sphingomyelin synthase

Overview: Following translocation from the ER to the Golgi under the influence of the ceramide transfer protein, sphingomyelin synthases allow the formation of sphingomyelin by the transfer of phosphocholine from the phospholipid phosphatidylcholine. Sphingomyelin synthase-related protein 1 is structurally related but lacks sphingomyelin synthase activity.

Nomenclature	sphingomyelin synthase 1	sphingomyelin synthase 2	sterile alpha motif domain containing 8
HGNC, UniProt	<i>SGMS1</i> , Q86VZ5	<i>SGMS2</i> , Q8NHU3	<i>SAMD8</i> , Q96LT4
EC number	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	2.7.8.27: ceramide + phosphatidylcholine -> sphingomyelin + diacylglycerol	2.7.8.-: ceramide + phosphatidylethanolamine -> ceramide phosphoethanolamine
Comments	–	Palmitoylation of sphingomyelin synthase 2 may allow targeting to the plasma membrane [476].	–

Sphingomyelin phosphodiesterase

Enzymes → Ceramide turnover → Sphingomyelin phosphodiesterase

Overview: Also known as sphingomyelinase.

Nomenclature	sphingomyelin phosphodiesterase 1, acid lysosomal	sphingomyelin phosphodiesterase 2, neutral membrane (neutral sphingomyelinase)	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)
HGNC, UniProt	<i>SMPD1</i> , P17405	<i>SMPD2</i> , O60906	<i>SMPD3</i> , Q9NY59
EC number	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.12: sphingomyelin -> ceramide + phosphocholine

Nomenclature	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	sphingomyelin phosphodiesterase, acid-like 3A	sphingomyelin phosphodiesterase, acid-like 3B
HGNC, UniProt	SMPD4 , Q9NXE4	SMPDL3A , Q92484	SMPDL3B , Q92485
EC number	3.1.4.12: sphingomyelin -> ceramide + phosphocholine	3.1.4.-: sphingomyelin -> ceramide + phosphocholine	3.1.4.-: sphingomyelin -> ceramide + phosphocholine

Neutral sphingomyelinase coupling factors

Enzymes → Ceramide turnover → Neutral sphingomyelinase coupling factors

Overview: Protein FAN [2] and polycomb protein EED [383] allow coupling between TNF receptors and neutral sphingomyelinase phosphodiesterases.

Nomenclature	embryonic ectoderm development	neutral sphingomyelinase (N-SMase) activation associated factor
HGNC, UniProt	EED , O75530	NSMAF , Q92636

Ceramide glucosyltransferase

Enzymes → Ceramide turnover → Ceramide glucosyltransferase

Nomenclature	UDP-glucose ceramide glucosyltransferase
HGNC, UniProt	UGCC , Q16739
EC number	2.4.1.80: UDP-glucose + ceramide = uridine diphosphate + glucosylceramide
Inhibitors	miglustat (p <i>K</i> _i 5.1) [53]
Comments	Glycoceramides are an extended family of sphingolipids, differing in the content and organization of the sugar moieties, as well as the acyl sidechains.

Acid ceramidase

Enzymes → Ceramide turnover → Acid ceramidase

Overview: The six human ceramidases may be divided on the basis of pH optima into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase (acid ceramidase) 1
HGNC, UniProt	ASAH1 , Q13510
EC number	3.5.1.23: ceramide → sphingosine + a fatty acid
Comments	This lysosomal enzyme is proteolysed to form the mature protein made up of two chains from the same gene product [261].

Neutral ceramidases

Enzymes → Ceramide turnover → Neutral ceramidases

Overview: The six human ceramidases may be divided on the basis of pH optima into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2B
HGNC, UniProt	ASAH2 , Q9NR71	ASAH2B , P0C7U1
EC number	3.5.1.23: ceramide → sphingosine + a fatty acid	–
Comments	The enzyme is associated with the plasma membrane [475].	–

Comments: ASAH2B appears to be an enzymatically inactive protein, which may result from gene duplication and truncation.

Alkaline ceramidases

Enzymes → Ceramide turnover → Alkaline ceramidases

Overview: The six human ceramidases may be divided on the basis of pH optima into acid, neutral and alkaline ceramidases, which also differ in their subcellular location.

Nomenclature	alkaline ceramidase 1	alkaline ceramidase 2	alkaline ceramidase 3
HGNC, UniProt	ACER1 , Q8TDN7	ACER2 , Q5QJU3	ACER3 , Q9NUN7
EC number	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.23: ceramide -> sphingosine + a fatty acid	3.5.1.-
Comments	ACER1 is associated with the ER [466].	ACER2 is associated with the Golgi apparatus [534].	ACER3 is associated with the ER and Golgi apparatus [314].

Ceramide kinase

Enzymes → Ceramide turnover → Ceramide kinase

Nomenclature	ceramide kinase
HGNC, UniProt	CERK , Q8TCT0
EC number	2.7.1.138: ceramide + ATP -> ceramide 1-phosphate + adenosine diphosphate
Inhibitors	NVP 231 (pIC ₅₀ 7.9) [178]

Comments: A ceramide kinase-like protein has been identified in the human genome ([CERKL](#), [Q49MI3](#)).

Further Reading

- Castro BM *et al.* (2014) Ceramide: a simple sphingolipid with unique biophysical properties. *Prog. Lipid Res.* **54**: 53-67 [PMID:24513486]
- Halmer R *et al.* (2014) Sphingolipids: important players in multiple sclerosis. *Cell. Physiol. Biochem.* **34**: 111-8 [PMID:24977485]
- Ito M *et al.* (2014) New insight into the structure, reaction mechanism, and biological functions of neutral ceramidase. *Biochim. Biophys. Acta* **1841**: 682-91 [PMID:24064302]
- Khavandgar Z *et al.* (2015) Sphingolipid metabolism and its role in the skeletal tissues. *Cell. Mol. Life Sci.* **72**: 959-69 [PMID:25424644]
- Lowther J *et al.* (2012) Structural, mechanistic and regulatory studies of serine palmitoyltransferase. *Biochem. Soc. Trans.* **40**: 547-54 [PMID:22616865]
- Saied EM *et al.* (2014) Small molecule inhibitors of ceramidases. *Cell. Physiol. Biochem.* **34**: 197-212 [PMID:24977492]

Chromatin modifying enzymes

Enzymes → Chromatin modifying enzymes

Overview: Chromatin modifying enzymes, and other chromatin-modifying proteins, fall into three broad categories: **writers**, **readers** and **erasers**. The function of these proteins is to dynamically maintain cell identity and regulate processes such as differentiation, development, proliferation and genome integrity *via* recognition of specific 'marks' (covalent post-translational modifications) on histone proteins and DNA [267]. In normal cells, tissues and organs, precise co-ordination of these proteins ensures expression of only those genes required to specify phenotype or which are required at specific times, for specific functions. Chromatin modifications allow DNA modifications not coded by the DNA sequence to be passed on through the genome and underlies heritable phenomena such as X chromosome inactivation, aging, heterochromatin formation, reprogramming, and gene silencing (epigenetic control). To date at least eight distinct types of modifications are found

on histones. These include small covalent modifications such as acetylation, methylation, and phosphorylation, the attachment of larger modifiers such as ubiquitination or sumoylation, and ADP ribosylation, proline isomerization and deimination. Chromatin modifications and the functions they regulate in cells are reviewed by Kouzarides (2007) [267].

Writer proteins include the histone methyltransferases, histone acetyltransferases, some kinases and ubiquitin ligases.

Readers include proteins which contain methyl-lysine-recognition motifs such as bromodomains, chromodomains, tudor domains, PHD zinc fingers, PWWP domains and MBT domains.

Erasers include the histone demethylases and histone deacetylases (HDACs and sirtuins).

Dysregulated epigenetic control can be associated with human diseases such as cancer [129], where a wide variety of cellular and pro-

tein aberrations are known to perturb chromatin structure, gene transcription and ultimately cellular pathways [24, 439]. Due to the reversible nature of epigenetic modifications, chromatin regulators are very tractable targets for drug discovery and the development of novel therapeutics. Indeed, small molecule inhibitors of writers (*e.g.* **azacitidine** and **decitabine** target the DNA methyltransferases DNMT1 and DNMT3 for the treatment of myelodysplastic syndromes [165, 520]) and erasers (*e.g.* the HDAC inhibitors **vorinostat**, **romidepsin** and **belinostat** for the treatment of T-cell lymphomas [144, 254]) are already being used in the clinic. The search for the next generation of compounds with improved specificity against chromatin-associated proteins is an area of intense basic and clinical research [56]. Current progress in this field is reviewed by Simó-Riudalbas and Esteller (2015) [440].

2.1.1.- Protein arginine N-methyltransferases

Enzymes → Chromatin modifying enzymes → 2.1.1.- Protein arginine N-methyltransferases

Overview: Protein arginine N-methyltransferases (PRMT, EC 2.1.1.-) encompass histone arginine N-methyltransferases (PRMT4, PRMT7, EC 2.1.1.125) and myelin basic protein N-methyltransferases (PRMT7, EC 2.1.1.126). They are dimeric

or tetrameric enzymes which use **S-adenosyl methionine** as a methyl donor, generating **S-adenosylhomocysteine** as a by-product. They generate both mono-methylated and dimethylated products; these may be symmetric (SDMA) or asym-

metric (**N^G,N^G-dimethyl-L-arginine**) versions, where both guanidine nitrogens are monomethylated or one of the two is dimethylated, respectively.

3.5.1.- Histone deacetylases (HDACs)

Enzymes → Chromatin modifying enzymes → 3.5.1.- Histone deacetylases (HDACs)

Overview: Histone deacetylases act as erasers of epigenetic acetylation marks on lysine residues in histones. Removal of the acetyl groups facilitates tighter packing of chromatin (heterochromatin formation) leading to transcriptional repression.

The histone deacetylase family has been classified in to five sub-families based on phylogenetic comparison with yeast homologues:

Class I contains HDACs 1, 2, 3 and 8
Class IIa contains HDACs 4, 5, 7 and 9
Class IIb contains HDACs 6 and 10

Class III contains the sirtuins (SIRT1-7)

Class IV contains only HDAC11.

Classes I, II and IV use Zn⁺ as a co-factor, whereas catalysis by Class III enzymes requires NAD⁺ as a co-factor, and members of this subfamily have ADP-ribosylase activity in addition to protein deacetylase function [420].

HDACs have more general protein deacetylase activity, being able to deacetylate lysine residues in non-histone proteins [82] such as microtubules [221], the hsp90 chaperone [268] and the tumour suppressor p53 [302].

Dysregulated HDAC activity has been identified in cancer cells and tumour tissues [288, 410], making HDACs attractive molecular targets in the search for novel mechanisms to treat cancer [522]. Several small molecule HDAC inhibitors are already approved for clinical use: **romidepsin**, **belinostat**, **vorinostat**, **panobinostat**, **belinostat**, **valproic acid** and **chidamide**. HDACs and HDAC inhibitors currently in development as potential anti-cancer therapeutics are reviewed by Simó-Riudalbas and Esteller (2015) [440].

Cyclic nucleotide turnover

Enzymes → Cyclic nucleotide turnover

Overview: Cyclic nucleotides are second messengers generated by cyclase enzymes from precursor triphosphates and hydrolysed by phosphodiesterases. The cellular actions of these cyclic nucleotides are mediated through activation of protein kinases (cAMP- and cGMP-dependent protein kinases), ion channels (cyclic nucleotide-gated, CNG, and hyperpolarization and cyclic nucleotide-gated, HCN) and guanine nucleotide exchange factors (GEFs, Epac).

Adenylyl cyclases

Enzymes → Cyclic nucleotide turnover → Adenylyl cyclases

Overview: Adenylyl cyclase, E.C. 4.6.1.1, converts ATP to cyclic AMP and pyrophosphate. Mammalian membrane-bound adenylyl cyclases are typically made up of two clusters of six TM domains separating two intracellular, overlapping catalytic domains that are the target for the nonselective activators forskolin, NKH477 (except AC9, [392]) and G α_s (the stimulatory G protein α subunit). Adenosine and its derivatives (e.g. 2',5'-dideoxyadenosine), acting through the P-site, appear to be physiological inhibitors of adenylyl cyclase activity [485]. Three families of adenylyl cyclase are distinguishable: calmodulin (CALM1 CALM2 CALM3, P62158)-stimulated (AC1, AC3 and AC8), Ca²⁺-inhibitable (AC5, AC6 and AC9) and Ca²⁺-insensitive (AC2, AC4 and AC7) forms.

Nomenclature	AC1	AC2	AC3	AC4	AC5
HGNC, UniProt	ADCY1, Q08828	ADCY2, Q08462	ADCY3, O60266	ADCY4, Q8NFM4	ADCY5, O95622
EC number	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1
Endogenous activators	calmodulin (CALM1 CALM2 CALM3, P62158), PKC-evoked phosphorylation [233, 474]	G $\beta\gamma$, PKC-evoked phosphorylation [73, 306, 478]	calmodulin (CALM1 CALM2 CALM3, P62158), PKC-evoked phosphorylation [81, 233]	G $\beta\gamma$ [163]	PKC-evoked phosphorylation [250]
Endogenous inhibitors	G α_i , G α_o , G $\beta\gamma$ [478, 479]	–	G α_i , RGS2, CaM kinase II-evoked phosphorylation [441, 479, 517]	PKC-evoked phosphorylation [554]	G α_i , Ca ²⁺ , PKA-evoked phosphorylation [227, 230, 479]
Selective inhibitors	–	–	–	–	NKY80 [364]

Nomenclature	AC6	AC7	AC8	AC9
HGNC, UniProt	ADCY6, O43306	ADCY7, P51828	ADCY8, P40145	ADCY9, O60503
EC number	4.6.1.1	4.6.1.1	4.6.1.1	4.6.1.1
Endogenous activators	–	PKC-evoked phosphorylation [516]	Ca ²⁺ [57]	–
Endogenous inhibitors	Gα _i , Ca ²⁺ , PKA-evoked phosphorylation, PKC-evoked phosphorylation [76, 275, 479, 541]	–	–	Ca ²⁺ /calcineurin [376]

Comments: Nitric oxide has been proposed to inhibit AC5 and AC6 selectively [210], although it is unclear whether this phenomenon is of physiological significance. A soluble adenylyl cyclase has been described ([ADCY10, Q96PN6](#) [48]), unaffected by either Gα or Gβγ subunits, which has been suggested to be a cytoplasmic bicarbonate (pH-insensitive) sensor [75]. It can be inhibited selectively by KH7 (pIC₅₀ 5.0–5.5) [208].

Soluble guanylyl cyclase

Enzymes → Cyclic nucleotide turnover → Soluble guanylyl cyclase

Overview: Soluble guanylyl cyclase (GTP diphosphate-lyase (cyclising)), E.C. 4.6.1.2, is a heterodimer comprising α and β chains, both of which have two subtypes in man (predominantly α1β1; [544]). A haem group is associated with the β chain and is the target for the endogenous ligand nitric oxide (NO•), and, potentially, carbon monoxide [150]. The enzyme converts [guanosine-5'-triphosphate](#) to the intracellular second messenger 3',5'-guanosine monophosphate ([cyclic GMP](#)).

Nomenclature	Soluble guanylyl cyclase
Common abbreviation	sGC
Subunits	Soluble guanylyl cyclase β 1 subunit , Soluble guanylyl cyclase α 1 subunit
EC number	4.6.1.2
Activators	isosorbide dinitrate , isosorbide mononitrate , nitroglycerin
Selective activators	BAY412272 [460], NO , YC1 [150], ataciguat [421], cinaciguat [461], riociguat [461]
Inhibitors	NS 2028 (pIC ₅₀ 8.1) [363] – Bovine
Selective inhibitors	ODQ (pIC ₅₀ 7.5) [167]

Subunits

Nomenclature	α 1 subunit	α 2 subunit	β 1 subunit	β 2 subunit
HGNC, UniProt	GUCY1A3 , Q02108	GUCY1A2 , P33402	GUCY1B3 , Q02153	GUCY1B2 , O75343

Comments: [ODQ](#) also shows activity at other haem-containing proteins [[134](#)], while [YC1](#) may also inhibit cGMP-hydrolysing phosphodiesterases [[149](#), [159](#)].

Exchange protein activated by cyclic AMP (Epac)

Enzymes → Cyclic nucleotide turnover → Exchange protein activated by cyclic AMP (Epac)

Overview: Epacs are members of a family of guanine nucleotide exchange factors ([ENSM0025000000899](#)), which also includes [RapGEF5](#) (GFR, [KIAA0277](#), MR-GEF, [Q92565](#)) and [RapGEFL1](#) (Link-GEFII, [Q9UHV5](#)). They are activated endogenously by [cyclic AMP](#) and with some pharmacological selectivity by [8-pCPT-2'-O-Me-cAMP](#) [[126](#)]. Once activated, Epacs induce an enhanced activity of the monomeric G proteins, Rap1 and Rap2 by facilitating binding of [guanosine-5'-triphosphate](#) in place of [guanosine 5'-diphosphate](#), leading to activation of [phospholipase C](#) [[423](#)].

Nomenclature	Epac1	Epac2
HGNC, UniProt	RAPGEF3 , O95398	RAPGEF4 , Q8WZA2
Inhibitors	–	HJC 0350 (pIC ₅₀ 6.5) [72], ESI-09 (pIC ₅₀ 4.4) [11]

Phosphodiesterases, 3',5'-cyclic nucleotide

Enzymes → Cyclic nucleotide turnover → Phosphodiesterases, 3',5'-cyclic nucleotide

Overview: 3',5'-Cyclic nucleotide phosphodiesterases (PDEs, 3',5'-cyclic-nucleotide 5'-nucleotidohydrolase), E.C. 3.1.4.17, catalyse the hydrolysis of a 3',5'-cyclic nucleotide (usually cyclic AMP or cyclic GMP). *Isobutylmethylxanthine* is a nonselective inhibitor with an IC₅₀ 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
HGNC, UniProt	<i>PDE1A</i> , P54750	<i>PDE1B</i> , Q01064	<i>PDE1C</i> , Q14123
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic GMP > cyclic AMP	cyclic GMP > cyclic AMP	cyclic GMP = cyclic AMP
Endogenous activators	calmodulin (<i>CALM1 CALM2 CALM3</i> , P62158)	calmodulin (<i>CALM1 CALM2 CALM3</i> , P62158)	calmodulin (<i>CALM1 CALM2 CALM3</i> , P62158)
Selective inhibitors	SCH51866 (pIC ₅₀ 7.2) [498], vinpocetine (pIC ₅₀ 5.1) [300]	SCH51866 (pIC ₅₀ 7.2) [498]	SCH51866 (pIC ₅₀ 7.2) [498], vinpocetine (pIC ₅₀ 4.3) [300]

Nomenclature	PDE2A	PDE3A	PDE3B
HGNC, UniProt	<i>PDE2A</i> , O00408	<i>PDE3A</i> , Q14432	<i>PDE3B</i> , Q13370
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic AMP ≫ cyclic GMP	–	–
Endogenous activators	cyclic GMP	–	–
Endogenous inhibitors	–	cyclic GMP (Selective)	cyclic GMP (Selective)
Inhibitors	milrinone (pIC ₅₀ <6.5) [465]	cilostazol (pIC ₅₀ 6.7) [465], inamrinone (pIC ₅₀ 4.8) [442]	–
Selective inhibitors	BAY607550 (pIC ₅₀ 8.3–8.8) [44], EHNA (pIC ₅₀ 5.3) [332]	cilostamide (pIC ₅₀ 7.5) [465], anagrelide (pIC ₅₀ 7.1–7.3) [245, 319, 326], milrinone (pIC ₅₀ 6.3–6.4) [123, 465]	cilostamide (pIC ₅₀ 7.3) [465], cilostazol (pIC ₅₀ 6.4) [465], milrinone (pIC ₅₀ 6) [465], inamrinone (pIC ₅₀ 4.5) [465]
Comments	EHNA is also an inhibitor of adenosine deaminase (E.C. 3.5.4.4).	–	–

Nomenclature	PDE4A	PDE4B	PDE4C	PDE4D	PDE5A
HGNC, UniProt	<i>PDE4A</i> , P27815	<i>PDE4B</i> , Q07343	<i>PDE4C</i> , Q08493	<i>PDE4D</i> , Q08499	<i>PDE5A</i> , O76074
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Activator	–	–	–	PKA-mediated phosphorylation [217]	Protein kinase A, protein kinase G [93]
Rank order of affinity	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic AMP ≫ cyclic GMP	cyclic GMP > cyclic AMP
Inhibitors	<i>ibudilast</i> (pIC ₅₀ 7.3) [262], <i>RS-25344</i> (pIC ₅₀ 7.2) [417]	<i>roflumilast</i> (pIC ₅₀ 9.4) [301], <i>ibudilast</i> (pIC ₅₀ 7.2) [262], <i>RS-25344</i> (pIC ₅₀ 6.5) [417]	<i>RS-25344</i> (pIC ₅₀ 8.1) [417], <i>ibudilast</i> (pIC ₅₀ 6.6) [262]	<i>RS-25344</i> (pIC ₅₀ 8.4) [417]	<i>gisadenafil</i> (pIC ₅₀ 8.9) [402], <i>milrinone</i> (pIC ₅₀ 7.3)
(Sub)family-selective inhibitors	<i>rolipram</i> (pIC ₅₀ 9) [508], <i>Ro20-1724</i> (pIC ₅₀ 6.5) [508]	<i>rolipram</i> (pIC ₅₀ 9) [508], <i>Ro20-1724</i> (pIC ₅₀ 6.4) [508]	<i>rolipram</i> (pIC ₅₀ 6.5) [508], <i>Ro20-1724</i> (pIC ₅₀ 5.4) [508]	<i>rolipram</i> (pIC ₅₀ 7.2) [508], <i>Ro20-1724</i> (pIC ₅₀ 6.2) [508]	–
Selective inhibitors	<i>YM976</i> (pIC ₅₀ 8.3) [13]	–	–	–	<i>ildenafil</i> (pIC ₅₀ 9.7) [47], <i>T0156</i> (pIC ₅₀ 9.5) [338], <i>sildenafil</i> (pIC ₅₀ 9) [494], <i>tadalafil</i> (pIC ₅₀ 8.5) [339], <i>SCH51866</i> (pIC ₅₀ 7.2) [498], <i>zaprinast</i> (pIC ₅₀ 6.8) [494]

Nomenclature	PDE6A	PDE6B	PDE6C	PDE6D	PDE6G	PDE6H
HGNC, UniProt	<i>PDE6A</i> , P16499	<i>PDE6B</i> , P35913	<i>PDE6C</i> , P51160	<i>PDE6D</i> , O43924	<i>PDE6G</i> , P18545	<i>PDE6H</i> , Q13956
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17

Nomenclature	PDE7A	PDE7B	PDE8A	PDE8B
HGNC, UniProt	<i>PDE7A</i> , Q13946	<i>PDE7B</i> , Q9NP56	<i>PDE8A</i> , O60658	<i>PDE8B</i> , O95263
EC number	3.1.4.17	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic AMP ≫ cyclic GMP [330]	cyclic AMP ≫ cyclic GMP [166]	cyclic AMP ≫ cyclic GMP [138]	cyclic AMP ≫ cyclic GMP [201]

(continued)				
Nomenclature	PDE7A	PDE7B	PDE8A	PDE8B
Inhibitors	–	BRL50481 (pIC ₅₀ 4.9) [7]	–	–
Selective inhibitors	BRL50481 (pIC ₅₀ 6.7–6.8) [7, 448]	dipyridamole (pIC ₅₀ 5.7–6) [166, 419], SCH51866 (pIC ₅₀ 5.8) [419]	dipyridamole (pIC ₅₀ 5.1) [138]	dipyridamole (pIC ₅₀ 4.3) [201]
Comments	–	–	PDE7A appears to be membrane-bound or soluble for PDE7A1 and 7A2 splice variants, respectively	–

Nomenclature	PDE9A	PDE10A	PDE11A
HGNC, UniProt	PDE9A , O76083	PDE10A , Q9Y233	PDE11A , Q9HCR9
EC number	3.1.4.17	3.1.4.17	3.1.4.17
Rank order of affinity	cyclic GMP ≫ cyclic AMP [137]	cyclic AMP , cyclic GMP [152]	cyclic AMP , cyclic GMP [133]
Inhibitors	–	–	tadalafil (pIC ₅₀ 6.5) [339], BC11-38 (pIC ₅₀ 6.5) [68]
Selective inhibitors	SCH51866 (pIC ₅₀ 5.8) [137], zaprinast (pIC ₅₀ 4.5) [137]	–	–

Comments: PDE1A, 1B and 1C appear to act as soluble homodimers, while PDE2A is a membrane-bound homodimer. PDE3A and PDE3B are membrane-bound.

PDE4 isoforms are essentially **cyclic AMP** 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 [212, 213]. PDE4A–D splice variants can be membrane-bound or cytosolic [217]. PDE4 isoforms may be labelled with [³H]rolipram.

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 **cyclic GMP** specific and is activated by the α -subunit of transducin ($G\alpha_t$) 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.

Further Reading

- Cooper DM *et al.* (2014) Adenylate cyclase-centred microdomains. *Biochem. J.* **462**: 199-213 [PMID:25102028]
- Derbyshire ER *et al.* (2012) Structure and regulation of soluble guanylate cyclase. *Annu. Rev. Biochem.* **81**: 533-59 [PMID:22404633]
- Francis SH *et al.* (2011) Mammalian cyclic nucleotide phosphodiesterases: molecular mechanisms and physiological functions. *Physiol. Rev.* **91**: 651-90 [PMID:21527734]
- Nicol X *et al.* (2014) Routes to cAMP: shaping neuronal connectivity with distinct adenylate cyclases. *Eur. J. Neurosci.* **39**: 1742-51 [PMID:24628976]
- Schmidt M *et al.* (2013) Exchange protein directly activated by cAMP (epac): a multidomain cAMP mediator in the regulation of diverse biological functions. *Pharmacol. Rev.* **65**: 670-709 [PMID:23447132]
- Steebhorn C. (2014) Structure, mechanism, and regulation of soluble adenylyl cyclases - similarities and differences to transmembrane adenylyl cyclases. *Biochim. Biophys. Acta* **1842**: 2535-47 [PMID:25193033]

Cytochrome P450

Enzymes → Cytochrome P450

Overview: The cytochrome P450 enzyme family (CYP450), E.C. 1.14.-.-, were originally defined by their strong absorbance at 450 nm due to the reduced carbon monoxide-complexed haem component of the cytochromes. They are an extensive family of haem-containing monooxygenases with a huge range of both endogenous and exogenous substrates. Listed below are the human enzymes; their relationship with rodent CYP450 enzyme activities is obscure in that the species orthologue may not mediate metabolism of the same substrates. Although the majority of CYP450 enzyme activities are concentrated in the liver, the extra-hepatic enzyme activities also contribute to patho/physiological processes. Genetic variation of CYP450 isoforms is widespread and likely underlies a significant proportion of the individual variation to drug administration. Further family members are included on the online database at www.GuidetoPHARMACOLOGY.org

CYP1 family

Enzymes → Cytochrome P450 → CYP1 family

Nomenclature	CYP1A1	CYP1A2	CYP1B1
HGNC, UniProt	CYP1A1, P04798	CYP1A2, P05177	CYP1B1, Q16678
EC number	1.14.1.1	1.14.1.1	1.14.1.1
Comments	–	–	Mutations have been associated with primary congenital glaucoma [464]

CYP2 family

Enzymes → Cytochrome P450 → CYP2 family

Nomenclature	CYP2A6	CYP2A7	CYP2C8
HGNC, UniProt	CYP2A6 , P11509	CYP2A7 , P20853	CYP2C8 , P10632
EC number	1.14.14.1	1.14.14.1	1.14.14.1
Comments	Metabolises nicotine	CYP2A7 does not incorporate haem and is functionally inactive [153]	Converts arachidonic acid to 11(R)-12(S)-epoxyeicosatrienoic acid or 14(R)-15(S)-epoxyeicosatrienoic acid [547].

Nomenclature	CYP2J2	CYP2R1
HGNC, UniProt	CYP2J2 , P51589	CYP2R1 , Q6VVX0
EC number	1.14.14.1	1.14.13.15
Comments	Converts arachidonic acid to 14(R)-15(S)-epoxyeicosatrienoic acid [531].	Converts vitamin D3 to 25-hydroxyvitamin D₃ [78].

CYP3 family

Enzymes → Cytochrome P450 → CYP3 family

Nomenclature	CYP3A4
HGNC, UniProt	CYP3A4 , P08684
EC number	1.14.13.32 : Albendazole + NADPH + O ₂ = albendazole S-oxide + NADP⁺ + H ₂ 1.14.13.157 : 1,8-cineole + NADPH + O ₂ = 2-exo-hydroxy-1,8-cineole + NADP⁺ + H ₂ O 1.14.13.97 : Taurochenodeoxycholate + NADPH + O ₂ = taurohyocholate + NADP⁺ + H ₂ O Lithocholate + NADPH + O ₂ = hyodeoxycholate + NADP⁺ + H ₂ O 1.14.13.67 : quinine + NADPH + O ₂ = 3-hydroxyquinine + NADP⁺ + H ₂ O ₂
Substrates	atorvastatin [140], codeine [140], diazepam [140], tamoxifen [140], erlotinib [140]

(continued)	
Nomenclature	CYP3A4
Products	4-hydroxy-tamoxifen quinone methide [432], 4-hydroxy-tamoxifen [432]
Comments	Metabolises a vast range of xenobiotics, including antidepressants, benzodiazepines, calcium channel blockers, and chemotherapeutic agents. CYP3A4 catalyses the 25-hydroxylation of trihydroxycholestane in liver microsomes [157].

CYP4 family

Enzymes → Cytochrome P450 → CYP4 family

Nomenclature	CYP4A11	CYP4F2	CYP4F3	CYP4F8	CYP4F12
HGNC, UniProt	CYP4A11 , Q02928	CYP4F2 , P78329	CYP4F3 , Q08477	CYP4F8 , P98187	CYP4F12 , Q9HCS2
EC number	1.14.15.3	1.14.13.30	1.14.13.30	1.14.14.1	1.14.14.1
Comments	Converts lauric acid to 12-hydroxylauric acid .	Responsible for ω -hydroxylation of LTB₄ , LXB₄ [335], and tocopherols, including vitamin E [453]	Responsible for ω -hydroxylation of LTB₄ , LXB₄ [335], and polyunsaturated fatty acids [135, 194]	Converts PGH₂ to 19-hydroxyPGH ₂ [54] and 8,9-EET or 11,12-EET to 18-hydroxy-8,9-EET or 18-hydroxy-11,12-EET [353].	AC004597.1 (ENSG00000225607) is described as being highly similar to CYP4F12

Nomenclature	CYP4F22	CYP4V2	CYP4X1	CYP4Z1
HGNC, UniProt	CYP4F22 , Q6NT55	CYP4V2 , Q6ZWL3	CYP4X1 , Q8N118	CYP4Z1 , Q86W10
EC number	1.14.14.-	1.14.-	1.14.14.1	1.14.14.1
Comments	Converts arachidonic acid to 16-HETE and 18-HETE [353].	Converts myristic acid to 14-hydroxymyristic acid [348].	Converts anandamide to 14,15-epoxyeicosatrienoic ethanolamide [459].	Converts lauric acid to 12-hydroxylauric acid

CYP5, CYP7 and CYP8 families

Enzymes → Cytochrome P450 → CYP5, CYP7 and CYP8 families

Nomenclature	CYP5A1	CYP8A1	CYP7A1	CYP7B1	CYP8B1
Common name	–	Prostacyclin synthase	–	–	–
HGNC, UniProt	TBXAS1 , P24557	PTGIS , Q16647	CYP7A1 , P22680	CYP7B1 , O75881	CYP8B1 , Q9UNU6
EC number	5.3.99.5: PGH ₂ = thromboxane A ₂	5.3.99.4	1.14.13.17	1.14.13.100	1.14.13.95
Comments	Inhibited by dazoxiben [398] and camonagrel [182].	Converts PGH ₂ to PGI ₂ [196]. Inhibited by tranylcypromine [181].	Converts cholesterol to 7 α -hydroxycholesterol [354].	Converts dehydroepiandrosterone to 7 α -DHEA [411].	Converts 7 α -hydroxycholest-4-en-3-one to 7- α ,12 α -dihydroxycholest-4-en-3-one (in rabbit) [226] in the biosynthesis of bile acids.

CYP11, CYP17, CYP19, CYP20 and CYP21 families

Enzymes → Cytochrome P450 → CYP11, CYP17, CYP19, CYP20 and CYP21 families

Nomenclature	CYP11A1	CYP11B1	CYP11B2	CYP17A1
Common name	–	–	Aldosterone synthase	–
HGNC, UniProt	CYP11A1 , P05108	CYP11B1 , P15538	CYP11B2 , P19099	CYP17A1 , P05093
EC number	1.14.15.6	1.14.15.4	1.14.15.4 1.14.15.5	1.14.99.9
Inhibitors	mitotane	metyrapone (pIC ₅₀ 7.8) [553], mitotane	osilodrostat (pIC ₅₀ 9.7) [537]	abiraterone (pIC ₅₀ 7.1–8.4) [386 , 390] galeterone (pIC ₅₀ 6.5) [192]
Selective inhibitors	–	–	–	–

(continued)				
Nomenclature	CYP11A1	CYP11B1	CYP11B2	CYP17A1
Comments	Converts cholesterol to pregnenolone plus 4-methylpentanal.	Converts deoxycortisone and 11-deoxycortisol to cortisone and cortisol , respectively. Loss-of-function mutations are associated with familial adrenal hyperplasia and hypertension. Inhibited by metyrapone [513]	Converts corticosterone to aldosterone	Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone , respectively. Converts 17α-hydroxypregnenolone and 17α-hydroxyprogesterone to dehydroepiandrosterone and androstenedione , respectively. Converts corticosterone to cortisol .

Nomenclature	CYP19A1	CYP20A1	CYP21A2
Common name	Aromatase	–	–
HGNC, UniProt	CYP19A1 , P11511	CYP20A1 , Q6UW02	CYP21A2 , P08686
EC number	1.14.14.1	1.14.--	1.14.99.10
Inhibitors	anastrozole (pIC ₅₀ 7.8) [343], aminoglutethimide [379]	–	–
Selective inhibitors	letrozole (pK _i 10.7) [323], exemestane (pIC ₅₀ 7.3) [85], testolactone (pK _i 4.5) [95]	–	–
Comments	Converts androstenedione and testosterone to estrone and 17β-estradiol , respectively. Inhibited by anastrozole [388], and letrozole [33]	–	Converts progesterone and 17α-hydroxyprogesterone to deoxycortisone and 11-deoxycortisol , respectively

CYP24, CYP26 and CYP27 families

Enzymes → Cytochrome P450 → CYP24, CYP26 and CYP27 families

Nomenclature	CYP24A1	CYP26A1	CYP26B1	CYP27A1	CYP27B1
Common abbreviation	–	–	–	Sterol 27-hydroxylase	–
HGNC, UniProt	CYP24A1 , Q07973	CYP26A1 , O43174	CYP26B1 , Q9NR63	CYP27A1 , Q02318	CYP27B1 , O15528
EC number	1.14.13.126	1.14.--	1.14.--	1.14.13.15	1.14.13.13

(continued)					
Nomenclature	CYP24A1	CYP26A1	CYP26B1	CYP27A1	CYP27B1
Comments	Converts 1,25-dihydroxyvitamin D₃ (calcitriol) to 1 α ,24R,25-trihydroxyvitamin D ₃ .	Converts retinoic acid to 4-hydroxyretinoic acid. Inhibited by liarozole	Converts retinoic acid to 4-hydroxyretinoic acid.	Converts cholesterol to 27-hydroxycholesterol .	Converts 25-hydroxyvitamin D ₃ to 1,25-dihydroxyvitamin D₃ (calcitriol)

CYP39, CYP46 and CYP51 families

Enzymes → Cytochrome P450 → CYP39, CYP46 and CYP51 families

Nomenclature	CYP39A1	CYP46A1	CYP51A1
Common abbreviation	–	Cholesterol 24-hydroxylase	Lanosterol 14- α -demethylase
HGNC, UniProt	CYP39A1 , Q9NYL5	CYP46A1 , Q9Y6A2	CYP51A1 , Q16850
EC number	1.14.13.99	1.14.13.98	–
Comments	Converts 24-hydroxycholesterol to 7 α ,24-dihydroxycholesterol [286].	Converts cholesterol to 24(S)-hydroxycholesterol .	Converts lanosterol to 4,4-dimethylcholesta-8.14.24-trienol.

Further Reading

- Guengerich FP *et al.* (2011) Orphans in the human cytochrome P450 superfamily: approaches to discovering functions and relevance in pharmacology. *Pharmacol. Rev.* **63**: 684-99 [[PMID:21737533](#)]
- Lorbek G *et al.* (2012) Cytochrome P450s in the synthesis of cholesterol and bile acids—from mouse models to human diseases. *FEBS J.* **279**: 1516-33 [[PMID:22111624](#)]
- Orr ST *et al.* (2012) Mechanism-based inactivation (MBI) of cytochrome P450 enzymes: structure-activity relationships and discovery strategies to mitigate drug-drug interaction risks. *J. Med. Chem.* **55**: 4896-933 [[PMID:22409598](#)]
- Peñas-Lledó EM *et al.* (2014) CYP2D6 variation, behaviour and psychopathology: implications for pharmacogenomics-guided clinical trials. *Br J Clin Pharmacol* **77**: 673-83 [[PMID:24033670](#)]
- Ross AC *et al.* (2011) Cytochrome P450s in the regulation of cellular retinoic acid metabolism. *Annu. Rev. Nutr.* **31**: 65-87 [[PMID:21529158](#)]
- Shahabi P *et al.* (2014) Human cytochrome P450 epoxygenases: variability in expression and role in inflammation-related disorders. *Pharmacol. Ther.* **144**: 134-61 [[PMID:24882266](#)]
- Werk AN *et al.* (2014) Functional gene variants of CYP3A4. *Clin. Pharmacol. Ther.* **96**: 340-8 [[PMID:24926778](#)]

Endocannabinoid turnover

Enzymes → Endocannabinoid turnover

Overview: The principle endocannabinoids are **2-arachidonoylglycerol** (2AG) and **anandamide** (N-arachidonylethanolamine, AEA), thought to be generated on demand rather than stored, although this may not always be the case [10]. Mechanisms for release and re-uptake of endocannabinoids (and related entities) are unclear, although candidates for intracellular transport have been suggested. For the generation of **2-arachidonoylglycerol**, the key enzyme in-

involved is diacylglycerol lipase (DGL), whilst several routes for **anandamide** synthesis have been described, the best characterized of which involves *N*-acylphosphatidylethanolamine-phospholipase D (NAPE-PLD, [438]). Inactivation of these endocannabinoids appears to occur predominantly through monoacylglycerol lipase (MGL) and fatty acid amide hydrolase (FAAH) for **2-arachidonoylglycerol** and **anandamide**, respectively. Note that these enzymes also contribute to the turnover of many

endogenous ligands inactive at CB₁ and CB₂ cannabinoid receptors, such as **N-oleylethanolamide**, **N-palmitoylethanolamine** and **2-oleoyl glycerol**. *In vitro* experiments indicate that the endocannabinoids are also substrates for oxidative metabolism *via* cyclooxygenase, lipoxygenase and cytochrome P450 enzyme activities [9, 145, 450].

Nomenclature	Diacylglycerol lipase α	Diacylglycerol lipase β	<i>N</i>-Acylphosphatidylethanolamine-phospholipase D
Common abbreviation	DGL α	DGL β	NAPE-PLD
HGNC, UniProt	<i>DAGLA</i>, Q9Y4D2	<i>DAGLB</i>, Q8NCG7	<i>NAPEPLD</i>, Q6IQ20
EC number	3.1.1.-	3.1.1.-	–
Selective inhibitors	orlistat (pIC ₅₀ 7.2) [37], RHC80267 (pIC ₅₀ 4.2) [243]	orlistat (pIC ₅₀ 7) [37], RHC80267	–
Comments	–	–	NAPE-PLD activity appears to be enhanced by polyamines in the physiological range [292], but fails to transphosphatidylate with alcohols [381] unlike phosphatidylcholine-specific phospholipase D.

Nomenclature	Monoacylglycerol lipase	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	<i>N</i>-Acylethanolamine acid amidase
Common abbreviation	MGL	FAAH	FAAH2	NAAA
HGNC, UniProt	<i>MGLL</i>, Q99685	<i>FAAH</i>, O00519	<i>FAAH2</i>, Q6GMR7	<i>NAAA</i>, Q02083
EC number	3.1.1.23	3.5.1.-	3.5.1.-	3.5.1.-
Rank order of affinity	2-oleoyl glycerol = 2-arachidonoylglycerol \gg anandamide [171]	anandamide > oleamide > N-oleylethanolamide > N-palmitoylethanolamine [518]	oleamide > N-oleylethanolamide > anandamide > N-palmitoylethanolamine [518]	N-palmitoylethanolamine > MEA > SEA \geq N-oleylethanolamide > anandamide [495]

(continued)				
Nomenclature	Monoacylglycerol lipase	Fatty acid amide hydrolase	Fatty acid amide hydrolase-2	N-Acylethanolamine acid amidase
Selective inhibitors	JZL184 (pIC ₅₀ 8.1) [295]	JNJ1661010 (pIC ₅₀ 7.8) [253], PF750 (pIC ₅₀ 6.3–7.8) [4], OL135 (pIC ₅₀ 7.4) [518], URB597 (pIC ₅₀ 6.3–7) [518], PF3845 (pIC ₅₀ 6.6) [5]	URB597 (pIC ₅₀ 7.5–8.3) [518], OL135 (pIC ₅₀ 7.9) [518]	S-OOPP (pIC ₅₀ 6.4) [451] – Rat, CCP (pIC ₅₀ 5.3) [492]

Comments: Many of the compounds described as inhibitors are irreversible and so potency estimates will vary with incubation time. FAAH2 is not found in rodents [518] and few of the inhibitors described have been assessed at this enzyme activity. **2-arachidonoylglycerol** has been reported to be hydrolysed by

multiple enzyme activities from neural preparations, including **ABHD6** (**Q9BV23**) [41], **ABHD12** (**8N2K0**) [41], neuropathy target esterase (**PNPLA6**, **Q8IY17**) [316] and carboxylesterase 1 (**CES1**, **P23141**) [533]. Although these have been incompletely defined, **WWL70** has been described to inhibit ABHD6 selectively with a

pIC₅₀ value of 7.2 [284]. Other selective inhibitors of NAAA (with respect to FAAH) have been described, but these are not yet commercially available.

Further Reading

- Blankman JL *et al.* (2013) Chemical probes of endocannabinoid metabolism. *Pharmacol. Rev.* **65**: 849-71 [PMID:23512546]
- Fowler CJ. (2013) Transport of endocannabinoids across the plasma membrane and within the cell. *FEBS J.* **280**: 1895-904 [PMID:23441874]
- Hermanson DJ *et al.* (2014) Substrate-selective COX-2 inhibition as a novel strategy for therapeutic endocannabinoid augmentation. *Trends Pharmacol. Sci.* **35**: 358-67 [PMID:24845457]
- Savinainen JR *et al.* (2012) The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. *Acta Physiol (Oxf)* **204**: 267-76 [PMID:21418147]

- Ueda N *et al.* (2013) Metabolism of endocannabinoids and related N-acylethanolamines: canonical and alternative pathways. *FEBS J.* **280**: 1874-94 [PMID:23425575]
- Wellner N *et al.* (2013) N-acylation of phosphatidylethanolamine and its biological functions in mammals. *Biochim. Biophys. Acta* **1831**: 652-62 [PMID:23000428]

Eicosanoid turnover

Enzymes → Eicosanoid turnover

Overview: Eicosanoids are 20-carbon fatty acids, where the usual focus is the polyunsaturated analogue **arachidonic acid** and its metabolites. Arachidonic acid is thought primarily to derive from **phospholipase A2** action on membrane phosphatidylcholine, and may be re-cycled to form phospholipid through con-

jugation with **coenzyme A** and subsequently glycerol derivatives. Oxidative metabolism of arachidonic acid is conducted through three major enzymatic routes: cyclooxygenases; lipoxygenases and cytochrome P450-like epoxygenases, particularly **CYP2J2**. Isoprostanes are structural analogues of the prostanoids (hence the

nomenclature D-, E-, F-isoprostanes and isothromboxanes), which are produced in the presence of elevated free radicals in a non-enzymatic manner, leading to suggestions for their use as biomarkers of oxidative stress. Molecular targets for their action have yet to be defined.

Cyclooxygenase

Enzymes → Eicosanoid turnover → Cyclooxygenase

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 PGG_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**, **indomethacin** and **paracetamol** (acetaminophen). PGH_2 may then be metabolised to prostaglandins and thromboxanes by various prostaglandin synthases in an apparently tissue-dependent manner.

Nomenclature	COX-1	COX-2
HGNC, UniProt	<i>PTGS1</i> , P23219	<i>PTGS2</i> , P35354
EC number	1.14.99.1: Hydrogen donor + arachidonic acid + 2O_2 = hydrogen acceptor + H_2O + PGH_2 arachidonic acid => PGG_2 => PGH_2 This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH_3	1.14.99.1: Hydrogen donor + arachidonic acid + 2O_2 = hydrogen acceptor + H_2O + PGH_2 arachidonic acid => PGG_2 => PGH_2 This enzyme is also associated with the following reaction:: docosahexaenoic acid => PGH_3
Inhibitors	bromfenac (pIC ₅₀ 8.1) [17], diclofenac (pIC ₅₀ 7.9) [556], meclofenamic acid (pIC ₅₀ 7.3) [247], flurbiprofen (pIC ₅₀ 7.1) [512], fenoprofen (pIC ₅₀ 6.8) [17], ketoprofen (pIC ₅₀ 6.5) [55], suprofen (pIC ₅₀ 6.2) [55],	benzquinamide (pIC ₅₀ 8.3) [17], flurbiprofen (pIC ₅₀ 8) [25], meclofenamic acid (pIC ₅₀ 7.4) [247], carprofen (pIC ₅₀ 7) [209], ketorolac (pIC ₅₀ 6.9) [503], nimesulide (pIC ₅₀ 6.2) [366], ketoprofen (pIC ₅₀ 6.2) [55],
Selective inhibitors	ketorolac (pIC ₅₀ 9.7) [512], FR122047 (pIC ₅₀ 7.5) [357]	celecoxib (pIC ₅₀ 8.7) [38], valdecoxib (pIC ₅₀ 8.3) [473], diclofenac (pIC ₅₀ 7.7) [42], rofecoxib (pIC ₅₀ 6.1–6.5) [512], lumiracoxib (pK _i 6.5) [43], meloxicam (pIC ₅₀ 6.3) [280], etoricoxib (pIC ₅₀ 6) [406]

Prostaglandin synthases

Enzymes → Eicosanoid turnover → Prostaglandin synthases

Overview: Subsequent to the formation of PGH_2 , the **cytochrome P450 activities** thromboxane synthase (CYP5A1, *TBXAS1*, P24557, EC 5.3.99.5) and prostacyclin synthase (CYP8A1, *PTGIS*, Q16647, EC 5.3.99.4) generate **thromboxane A₂** and prostacyclin (**PGI₂**), respectively. Additionally, multiple en-

zyme activities are able to generate prostaglandin E₂ (**PGE₂**), prostaglandin D₂ (**PGD₂**) and prostaglandin F_{2α} (**PGF_{2α}**). **PGD₂** can be metabolised to 9α,11β-prostacyclin F_{2α} through the multi-functional enzyme activity of AKR1C3. **PGE₂** can be metabolised to 9α,11β-prostaglandin F_{2α} through the 9-ketoreductase activity

of CBR1. Conversion of the 15-hydroxyecosanoids, including prostaglandins, lipoxins and leukotrienes to their keto derivatives by the NAD-dependent enzyme HPGD leads to a reduction in their biological activity.

Nomenclature	CYP5A1	CYP8A1	mPGES1	mPGES2	cPGES
Common name	–	Prostacyclin synthase	–	–	–
HGNC, UniProt	TBXAS1, P24557	PTGIS, Q16647	PTGES, O14684	PTGES2, Q9H7Z7	PTGES3, Q15185
EC number	5.3.99.5: PGH₂ = thromboxane A₂	5.3.99.4	5.3.99.3: PGH₂ = PGE₂	5.3.99.3: PGH₂ = PGE₂	5.3.99.3: PGH₂ = PGE₂
Cofactors	–	–	glutathione	dihydrolipoic acid	–
Comments	Inhibited by dazoxiben [398] and camonagrel [182] .	Converts PGH₂ to PGI₂ [196]. Inhibited by tranylcypromine [181]	–	–	Phosphorylated and activated by casein kinase 2 (CK2) [260]. Appears to regulate steroid hormone function by interaction with dimeric hsp90 [69 , 241].

Nomenclature	L-PGDS	H-PGDS	AKR1C3	CBR1	HPGD
HGNC, UniProt	PTGDS, P41222	HPGDS, O60760	AKR1C3, P42330	CBR1, P16152	HPGD, P15428
EC number	5.3.99.2: PGH₂ = PGD₂	5.3.99.2: PGH₂ = PGD₂	1.3.1.20 1.1.1.188: PGD₂ + NADP⁺ = PGF_{2α} + NADPH + H⁺ 1.1.1.64 1.1.1.239 1.1.1.213	1.1.1.184 1.1.1.189: PGE₂ + NADP⁺ = PGF_{2α} + NADPH + H⁺ 1.1.1.197	1.1.1.141 15-hydroxyprostaglandins => 15-ketoprostaglandins LXA₄ => 15-keto-lipoxin A₄
Inhibitors	–	–	flufenamic acid, indomethacin, flavonoids [321, 446]	–	–
Cofactors	–	–	NADP⁺	NADP⁺	–
Inhibitors	–	HQL-79 (pIC₅₀ 5.3–5.5) [15]	–	wedelolactone (pIC₅₀ 5.4) [555]	–
Comments	–	–	Also acts as a hydroxysteroid dehydrogenase activity.	–	–

Comments: [YS121](#) has been reported to inhibit mPGES1 and 5-LOX with a pIC₅₀ value of 5.5 [[263](#)].

Lipoxygenases

Enzymes → Eicosanoid turnover → Lipoxygenases

Overview: The lipoxygenases (LOXs) are a structurally related family of non-heme iron dioxygenases that function in the production, and in some cases metabolism, of fatty acid hydroperoxides. For **arachidonic acid** as substrate, these products are hydroperoxyeicosatetraenoic acids (HPETEs). In humans there are five lipoxygenases, the 5S-(arachidonate : oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate : oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate : oxygen 15-oxidoreductase) LOXs that oxygenate arachidonic acid in different positions along the carbon chain and form the corresponding 5S-, 12S-, 12R-, or 15S-hydroperoxides, respectively.

Nomenclature	5-LOX	12R-LOX	12S-LOX	15-LOX-1	15-LOX-2	E-LOX
HGNC, UniProt	ALOX5 , P09917	ALOX12B , O75342	ALOX12 , P18054	ALOX15 , P16050	ALOX15B , O15296	ALOXE3 , Q9BYJ1
EC number	1.13.11.34: arachidonic acid + O ₂ = LTA ₄ + H ₂ O	1.13.11.31 arachidonic acid + O ₂ => 12R-HPETE	1.13.11.31 arachidonic acid + O ₂ => 12S-HPETE	1.13.11.33: arachidonic acid + O ₂ = 15S-HPETE linoleic acid + O ₂ => 13S-HPODE	1.13.11.33: arachidonic acid + O ₂ = 15S-HPETE	1.13.11.-
Endogenous inhibitor	Protein kinase A-mediated phosphorylation [304]	–	–	–	–	–
Substrates	–	–	methyl arachidonate	–	–	–
Endogenous substrates	arachidonic acid	–	–	–	–	12R-HPETE
Endogenous activators	5-LOX activating protein (ALOX5AP , P20292)	–	–	–	–	–
Selective inhibitors	CJ13610 (pIC ₅₀ 7.2) [136], zileuton	–	–	–	–	–
Comments	FLAP activity can be inhibited by MK-886 [116] and BAY-X1005 [197] leading to a selective inhibition of 5-LOX activity	–	–	–	–	E-LOX metabolises the product from the 12R-lipoxygenase (12R-HPETE) to a specific epoxyalcohol compound [543].

Comments: An 8-LOX (EC 1.13.11.40, arachidonate:oxygen 8-oxidoreductase) may be the mouse orthologue of 15-LOX-2 [158]. Some general LOX inhibitors are **nordihydroguaiaretic acid** and **esculetin**. **Zileuton** and **caffeic acid** are used as 5-lipoxygenase inhibitors, 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 [414].

Leukotriene and lipoxin metabolism

Enzymes → Eicosanoid turnover → Leukotriene and lipoxin metabolism

Overview: Leukotriene A₄ (LTA₄), produced by 5-LOX activity, and lipoxins may be subject to further oxidative metabolism; ω-hydroxylation is mediated by CYP4F2 and CYP4F3, while β-oxidation in mitochondria and peroxisomes proceeds in a manner dependent on coenzyme A conjugation. Conjugation of LTA₄ at the 6 position with reduced glutathione to generate LTC₄ occurs under the influence of leukotriene C₄ synthase, with the subsequent formation of LTD₄ and LTE₄, all three of which are

agonists at CysLT receptors. LTD₄ formation is catalysed by γ-glutamyltransferase, and subsequently dipeptidase 2 removes the terminal glycine from LTD₄ to generate LTE₄. Leukotriene A₄ hydrolase converts the 5,6-epoxide LTA₄ to the 5-hydroxylated LTB₄, an agonist for BLT receptors. LTA₄ is also acted upon by 12S-LOX to produce the trihydroxyeicosatetraenoic acids lipoxins LXA₄ and LXB₄. Treatment with a LTA₄ hydrolase inhibitor in a murine model of allergic airway inflammation increased LXA₄

levels, in addition to reducing LTB₄, in lung lavage fluid [400]. LTA₄ hydrolase is also involved in biosynthesis of resolvin Es. Aspirin has been reported to increase endogenous formation of 18S-hydroxyeicosapentaenoate (18S-HEPE) compared with 18R-HEPE, a resolvin precursor. Both enantiomers may be metabolised by human recombinant 5-LOX; recombinant LTA₄ hydrolase converted chiral 5S(6)-epoxide-containing intermediates to resolvin E1 and 18S-resolvin E1 [358].

Nomenclature	Leukotriene C ₄ synthase	γ-Glutamyltransferase	Dipeptidase 1	Dipeptidase 2
HGNC, UniProt	LTC4S, Q16873	GGCT, O75223	DPEP1, P16444	DPEP2, Q9H4A9
EC number	4.4.1.20: LTC ₄ = glutathione + LTA ₄	2.3.2.2: (5-L-glutamyl)-peptide + an amino acid = a peptide + a 5-L-glutamyl amino acid LTC ₄ + H ₂ O => LTD ₄ + L-glutamate	3.4.13.19: LTD ₄ + H ₂ O = LTE ₄ + glycine	3.4.13.19: LTD ₄ + H ₂ O = LTE ₄ + glycine
Inhibitors	–	–	cilastatin (pK _i 6) [179] – Unknown	–

Comments: LTA₄H is a member of a family of arginyl aminopeptidases (ENFSM0025000001675), which also includes aminopep-

tidase B (RNPEP, 9H4A4) and aminopeptidase B-like 1 (RNPEPL1, Q9HAU8). Dipeptidase 1 and 2 are members of a family of mem-

brane dipeptidases, which also includes (DPEP3, Q9H4B8) for which LTD₄ appears not to be a substrate.

Further Reading

- Durand T *et al.* (2011) Isoprostanes and phytoprostanes: Bioactive lipids. *Biochimie* **93**: 52-60 [PMID:20594988]
- Floyd CN *et al.* (2014) Mechanisms of aspirin resistance. *Pharmacol. Ther.* **141**: 69-78 [PMID:23993980]
- Haeggström JZ *et al.* (2011) Lipoxygenase and leukotriene pathways: biochemistry, biology, and roles in disease. *Chem. Rev.* **111**: 5866-98 [PMID:21936577]
- Korotkova M *et al.* (2014) Persisting eicosanoid pathways in rheumatic diseases. *Nat Rev Rheumatol* **10**: 229-41 [PMID:24514915]
- Krieg P *et al.* (2014) The role of lipoxygenases in epidermis. *Biochim. Biophys. Acta* **1841**: 390-400 [PMID:23954555]
- Rodríguez M *et al.* (2014) Polarization of the innate immune response by prostaglandin E2: a puzzle of receptors and signals. *Mol. Pharmacol.* **85**: 187-97 [PMID:24170779]
- Smith WL *et al.* (2011) Enzymes of the cyclooxygenase pathways of prostanoid biosynthesis. *Chem. Rev.* **111**: 5821-65 [PMID:21942677]
- Tai HH *et al.* (2011) Regulation of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) by non-steroidal anti-inflammatory drugs (NSAIDs). *Prostaglandins Other Lipid Mediat.* **96**: 37-40 [PMID:21763448]

GABA turnover

Enzymes → GABA turnover

Overview: The inhibitory neurotransmitter γ -aminobutyrate (GABA, 4-aminobutyrate) is generated in neurones by glutamic acid decarboxylase. GAD1 and GAD2 are differentially expressed during development, where GAD2 is thought to subserve a trophic role in early life and is distributed throughout the cytoplasm. GAD1 is expressed in later life and is more associated with nerve

terminals [128] where GABA is principally accumulated in vesicles through the action of the vesicular inhibitory amino acid transporter [SLC32A1](#). The role of γ -aminobutyraldehyde dehydrogenase (ALDH9A1) in neurotransmitter GABA synthesis is less clear. Following release from neurons, GABA may interact with either GABA_A or GABA_B receptors and may be accumu-

lated in neurones and glia through the action of members of the [SLC6 family of transporters](#). Successive metabolism through GABA transaminase and succinate semialdehyde dehydrogenase generates succinic acid, which may be further metabolized in the mitochondria in the tricarboxylic acid cycle.

Nomenclature	Glutamic acid decarboxylase 1, decarboxylase 2	aldehyde dehydrogenase 9 family, member A1	4-aminobutyrate aminotransferase	aldehyde dehydrogenase 5 family, member A1
Common abbreviation	GAD1, GAD2	–	GABA-T	SSADH
HGNC, UniProt	GAD1 , Q99259 , GAD2 , Q05329	ALDH9A1 , P49189	ABAT , P80404	ALDH5A1 , P51649
EC number	4.1.1.15: L-glutamic acid + H ⁺ → GABA + CO ₂	1.2.1.19: 4-aminobutanal + NAD + H ₂ O = GABA + NADH + H ⁺ 1.2.1.47: 4-trimethylammoniumbutanal + NAD + H ₂ O = 4-trimethylammoniumbutanoate + NADPH + 2H ⁺ 1.2.1.3: an aldehyde + H ₂ O + NAD = a carboxylate + 2H ⁺ + NADH	2.6.1.19: GABA + α -ketoglutaric acid = L-glutamic acid + 4-oxobutanoate 2.6.1.22: (S)-3-amino-2-methylpropanoate + α -ketoglutaric acid = 2-methyl-3-oxopropanoate + L-glutamic acid	1.2.1.24: 4-oxobutanoate + NAD + H ₂ O = succinic acid + NADH + 2H ⁺ 4-hydroxy-trans-2-nonenal + NAD + H ₂ O = 4-hydroxy-trans-2-nonenal + NADH + 2H ⁺
Endogenous substrates	L-glutamic acid, L-aspartic acid	–	–	–
Products	GABA	–	–	–
Cofactors	pyridoxal phosphate	NAD	pyridoxal phosphate	NAD [432]
Inhibitors	–	–	vigabatrin (Irreversible inhibition) (pK _i 3.1) [289, 437]	–
Selective inhibitors	s-allylglycine	–	–	–
Comments	L-aspartic acid is a less rapidly metabolised substrate of mouse brain glutamic acid decarboxylase generating β -alanine [530]. Autoantibodies against GAD1 and GAD2 are elevated in type 1 diabetes mellitus and neurological disorders (see Further reading).	–	–	–

Further Reading

- Errichiello L *et al.* (2011) Temporal lobe epilepsy and anti glutamic acid decarboxylase autoimmunity. *Neurol. Sci.* **32**: 547-50 [PMID:21468678]
- Kim KJ *et al.* (2011) Succinic semialdehyde dehydrogenase: biochemical-molecular-clinical disease mechanisms, redox regulation, and functional significance. *Antioxid. Redox Signal.* **15**: 691-718 [PMID:20973619]
- McQuail JA *et al.* (2015) Molecular aspects of age-related cognitive decline: the role of GABA signalling. *Trends Mol Med* **21**: 450-60 [PMID:26070271]
- Pan ZZ. (2012) Transcriptional control of Gad2. *Transcription* **3**: 68-72 [PMID:22414751]
- Verrotti A *et al.* (2012) Seizures and type 1 diabetes mellitus: current state of knowledge. *Eur. J. Endocrinol.* **167**: 749-58 [PMID:22956556]

Glycerophospholipid turnover

Enzymes → Glycerophospholipid turnover

Overview: Phospholipids are the basic barrier components of membranes in eukaryotic cells divided into glycerophospholipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylinositol and its phosphorylated derivatives) and sphingolipids (ceramide phosphorylcholine and ceramide phosphorylethanolamine).

Phosphatidylinositol kinases

Enzymes → Glycerophospholipid turnover → Phosphatidylinositol kinases

Overview:

Phosphatidylinositol may be phosphorylated at either 3- or 4- positions on the inositol ring by PI 3-kinases or PI 4-kinases, respectively.

Phosphatidylinositol 3-kinases

Phosphatidylinositol 3-kinases (PI3K, provisional nomenclature) catalyse the introduction of a phosphate into the 3-position of phosphatidylinositol (PI), phosphatidylinositol 4-phosphate (PIP) or phosphatidylinositol 4,5-bisphosphate (PIP₂). There is evidence that PI3K can also phosphorylate serine/threonine residues on proteins. In addition to the classes described below, further serine/threonine protein kinases, including ATM (Q13315) and mTOR (P42345), have been described to phosphorylate phosphatidylinositol and have been termed PI3K-related kinases. Structurally, PI3K have common motifs of at

least one C2, calcium-binding domain and helical domains, alongside structurally-conserved catalytic domains. Wortmannin and LY294002 are widely-used inhibitors of PI3K activities. Wortmannin is irreversible and shows modest selectivity between Class I and Class II PI3K, while LY294002 is reversible and selective for Class I compared to Class II PI3K.

Class I PI3Ks (EC 2.7.1.153) phosphorylate phosphatidylinositol 4,5-bisphosphate to generate phosphatidylinositol 3,4,5-trisphosphate and are heterodimeric, matching catalytic and regulatory subunits. Class IA PI3Ks include p110 α , p110 β and p110 δ catalytic subunits, with predominantly p85 and p55 regulatory subunits. The single catalytic subunit that forms Class IB PI3K is p110 γ . Class IA PI3Ks are more associated with receptor tyrosine kinase pathways, while the Class IB PI3K is linked more with GPCR signalling.

Class II PI3Ks (EC 2.7.1.154) phosphorylate phosphatidylinositol to generate phosphatidylinositol 3-phosphate (and possibly phosphatidylinositol 4-phosphate to generate phosphatidylinositol 3,4-bisphosphate). Three monomeric members exist, PI3K-C2 α , β and γ , and include Ras-binding, Phox homology and two C2 domains.

The only **class III PI3K** isoform (EC 2.7.1.137) is a heterodimer formed of a catalytic subunit (VPS34) and regulatory subunit (VPS15).

Phosphatidylinositol 4-kinases

Phosphatidylinositol 4-kinases (EC 2.7.1.67) generate phosphatidylinositol 4-phosphate and may be divided into higher molecular weight type III and lower molecular weight type II forms.

1-phosphatidylinositol 4-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → 1-phosphatidylinositol 4-kinase family

Nomenclature	phosphatidylinositol 4-kinase, catalytic, alpha	phosphatidylinositol 4-kinase, catalytic, beta
Common abbreviation	PI4KIII α /PIK4CA	PI4KIII β /PIK4CB
HGNC, UniProt	<i>PI4KA</i> , P42356	<i>PI4KB</i> , Q9UBF8
EC number	2.7.1.67	2.7.1.67
Endogenous activation	–	PKD-mediated phosphorylation [199]
(Sub)family-selective inhibitors	wortmannin (pIC ₅₀ 6.7–6.8) [170, 329]	wortmannin (pIC ₅₀ 6.7–6.8) [170, 329]
Selective inhibitors	–	PIK-93 [259]

Phosphatidylinositol-4-phosphate 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol-4-phosphate 3-kinase family

Nomenclature	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 beta	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 gamma
Common abbreviation	C2 α /PIK3C2A	C2 β /PIK3C2B	C2 γ /PIK3C2G
HGNC, UniProt	<i>PIK3C2A</i> , O00443	<i>PIK3C2B</i> , O00750	<i>PIK3C2G</i> , O75747
EC number	2.7.1.154	2.7.1.154	2.7.1.154

Phosphatidylinositol 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol 3-kinase family

Nomenclature	phosphatidylinositol 3-kinase, catalytic subunit type 3
Common abbreviation	VPS34/PIK3C3
HGNC, UniProt	<i>PIK3C3</i> , Q8NEB9
EC number	2.7.1.137

Phosphatidylinositol-4,5-bisphosphate 3-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Phosphatidylinositol-4,5-bisphosphate 3-kinase family

Nomenclature	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit beta	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta
Common abbreviation	p110 α /PIK3CA	p110 β /PIK3CB	p110 γ /PIK3CG	p110 δ /PIK3CD
HGNC, UniProt	<i>PIK3CA</i> , P42336	<i>PIK3CB</i> , P42338	<i>PIK3CG</i> , P48736	<i>PIK3CD</i> , O00329
EC number	2.7.1.153 2.7.11.1	2.7.1.153	2.7.1.153	2.7.1.153
Inhibitors	<i>PIK-75</i> (pIC ₅₀ 9.5) [200], <i>gedatolisib</i> (pIC ₅₀ 9.4) [500], <i>PF-04691502</i> (pK _i 9.2) [290], <i>PI-103</i> (pIC ₅₀ 8.7) [404], <i>BGT-226</i> (pIC ₅₀ 8.4) [315], <i>KU-0060648</i> (pIC ₅₀ 8.4) [60], <i>dactolisib</i> (pIC ₅₀ 8.4) [310], <i>apitolisib</i> (pIC ₅₀ 8.3) [467], <i>alpelisib</i> (pIC ₅₀ 8.3) [155], <i>PIK-75</i> (pIC ₅₀ 8.2) [259], <i>buparlisib</i> (pIC ₅₀ 7.5) [49], <i>PP121</i> (pIC ₅₀ 7.3) [14]	<i>KU-0060648</i> (pIC ₅₀ 9.3) [60], <i>PI-103</i> (pIC ₅₀ 8.5) [404], <i>AZD6482</i> (pIC ₅₀ 8) [355], <i>ZSTK474</i> (pIC ₅₀ 7.8) [535], <i>apitolisib</i> (pIC ₅₀ 7.6) [467], <i>BGT-226</i> (pIC ₅₀ 7.2) [315]	<i>dactolisib</i> (pIC ₅₀ 8.3) [310], <i>apitolisib</i> (pIC ₅₀ 7.8) [467], <i>PI-103</i> (pIC ₅₀ 7.8) [404], <i>BGT-226</i> (pIC ₅₀ 7.4) [315], <i>ZSTK474</i> (pIC ₅₀ 7.3) [535], <i>TG-100-115</i> (pIC ₅₀ 7.1) [369], <i>alpelisib</i> (pIC ₅₀ 6.6) [155], <i>KU-0060648</i> (pIC ₅₀ 6.2) [60]	<i>KU-0060648</i> (pIC ₅₀ >10) [60], <i>idelalisib</i> (<i>in vitro</i> activity against recombinant enzyme) (pIC ₅₀ 8.6) [276], <i>PI-103</i> (pIC ₅₀ 8.5) [404], <i>ZSTK474</i> (pIC ₅₀ 8.2) [535], <i>apitolisib</i> (pIC ₅₀ 8.2) [467], <i>dactolisib</i> (pIC ₅₀ 8.1) [310], <i>alpelisib</i> (pIC ₅₀ 6.5) [155]

(continued)				
Nomenclature	phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha	phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit beta	phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit gamma	phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit delta
(Sub)family-selective inhibitors	pictilisib (pIC ₅₀ 8.5) [141]	pictilisib (pIC ₅₀ 7.5) [141]	pictilisib (pIC ₅₀ 7.1) [141]	pictilisib (pIC ₅₀ 8.5) [141]
Selective inhibitors	–	–	CZC 24832 (pK _d 7.7) [30], CZC 24832 (pIC ₅₀ 7.6) [30]	–

1-phosphatidylinositol-3-phosphate 5-kinase family

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → 1-phosphatidylinositol-3-phosphate 5-kinase family

Nomenclature	phosphoinositide kinase, FYVE finger containing
HGNC, UniProt	PIKFYVE, Q9Y217-4
EC number	2.7.1.150: ATP + 1-phosphatidyl-1D-myo-inositol 3-phosphate = ADP + 1-phosphatidyl-1D-myo-inositol 3,5-bisphosphate

Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Type I PIP kinases (1-phosphatidylinositol-4-phosphate 5-kinase family)

Overview: Type I PIP kinases are required for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P₂) by phosphorylating PtdIns(4)P [397]. This enzyme family is also known as type I PIP(5)Ks.

Nomenclature	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha	phosphatidylinositol-4-phosphate 5-kinase, type I, gamma
Common abbreviation	PIP5K1A	PIP5K1C
HGNC, UniProt	PIP5K1A, Q99755	PIP5K1C, O60331

(continued)		
Nomenclature	phosphatidylinositol-4-phosphate 5-kinase, type I, alpha	phosphatidylinositol-4-phosphate 5-kinase, type I, gamma
EC number	2.7.1.68	2.7.1.68
Inhibitors	ISA-2011B [428]	–

Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Enzymes → Kinases (EC 2.7.x.x) → Lipid modifying kinases → Type II PIP kinases (1-phosphatidylinositol-5-phosphate 4-kinase family)

Overview: Type II PIP kinases are essential for the production of the second messenger phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P₂) by phosphorylating PtdIns(5)P [397]. This enzyme family is also known as type II PIP(5)Ks.

Nomenclature	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	phosphatidylinositol-5-phosphate 4-kinase, type II, beta	phosphatidylinositol-5-phosphate 4-kinase, type II, gamma
Common abbreviation	–	PIP4K2B	PIP4K2C
HGNC, UniProt	PIP4K2A, P48426	PIP4K2B, P78356	PIP4K2C, Q8TBX8
EC number	2.7.1.149	2.7.1.149	2.7.1.149
	ATP + 1-phosphatidyl-1D- <i>myo</i> -inositol 5-phosphate <=> ADP + 1-phosphatidyl-1D- <i>myo</i> -inositol 4,5-bisphosphate		

Further Reading

Neubauer HA *et al.* (2013) Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS J.* **280**: 5317-36 [PMID:23638983] Truman JP *et al.* (2014) Evolving concepts in cancer therapy through targeting sphingolipid metabolism. *Biochim. Biophys. Acta* **1841**: 1174-88 [PMID:24384461]

Phosphoinositide-specific phospholipase C

Enzymes → Glycerophospholipid turnover → Phosphoinositide-specific phospholipase C

Overview: Phosphoinositide-specific phospholipase C (PLC, EC 3.1.4.11), catalyses the hydrolysis of PIP₂ to IP₃ and 1,2-diaclyglycerol, 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 are activated primarily by G protein-coupled receptors through members of the G_{q/11} family of G proteins. The receptor-

mediated activation of PLC-γ involves their phosphorylation by receptor tyrosine kinases (RTK) 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 G protein-coupled and catalytic receptors. Ca²⁺ 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 *m3M3FBS* [21], although this mechanism of action has been questioned [271]. The aminosteroid *U73122* has been described as an inhibitor of phosphoinositide-specific PLC [447], although its selectivity among the isoforms is untested and it has been reported to occupy the H1 histamine receptor [222].

Nomenclature	PLCβ1	PLCβ2	PLCβ3	PLCβ4	PLCγ1	PLCγ2
HGNC, UniProt	<i>PLCB1</i> , Q9NQ66	<i>PLCB2</i> , Q00722	<i>PLCB3</i> , Q01970	<i>PLCB4</i> , Q15147	<i>PLCG1</i> , P19174	<i>PLCG2</i> , P16885
Endogenous activators	Gαq, Gα11, Gβγ [207, 374, 449]	Gα16, Gβγ, Rac2 (<i>RAC2</i> , P15153) [59, 223, 224, 281, 374]	Gαq, Gβγ [65, 281, 374]	Gαq [237]	PIP ₃ [20]	PIP ₃ , Rac1 (<i>RAC1</i> , P63000), Rac2 (<i>RAC2</i> , P15153), Rac3 (<i>RAC3</i> , P60763) [20, 384, 507]

Nomenclature	PLCδ1	PLCδ3	PLCδ4	PLCε1	PLCζ1	PLCη1	PLCη2
HGNC, UniProt	<i>PLCD1</i> , P51178	<i>PLCD3</i> , Q8N3E9	<i>PLCD4</i> , Q9BRC7	<i>PLCE1</i> , Q9P212	<i>PLCZ1</i> , Q86YW0	<i>PLCH1</i> , Q4KWH8	<i>PLCH2</i> , O75038
Endogenous activators	Transglutaminase II, p122-RhoGAP {Rat}, spermine, Gβγ [187, 214, 344, 374]	–	–	Ras, rho [452, 525]	–	–	Gβγ [551]
Endogenous inhibitors	Sphingomyelin [378]	–	–	–	–	–	–

Comments: A series of PLC-like proteins (*PLCL1*, Q15111; *PLCL2*, Q9UPRO and *PLCH1*, Q4KWH8) form a family with PLCδ and PLCζ1 isoforms, but appear to lack catalytic activity. PLC-δ2 has been cloned from bovine sources [328].

Phospholipase A₂

Enzymes → Glycerophospholipid turnover → Phospholipase A₂

Overview: Phospholipase A₂ (PLA₂, EC 3.1.1.4) cleaves the *sn*-2 fatty acid of phospholipids, primarily phosphatidylcholine, to generate **lysophosphatidylcholine** and **arachidonic acid**. Most commonly-used inhibitors (*e.g.* **bromo-enol lactone**, **arachidonyl trifluoromethyl ketone** or **methyl arachidonyl fluorophosphonate**) are either non-selective within the family of phospholipase A₂ enzymes or have activity against other eicosanoid-metabolising enzymes.

Secreted or extracellular forms: sPLA₂-1B, sPLA₂-2A, sPLA₂-2D, sPLA₂-2E, sPLA₂-2F, sPLA₂-3, sPLA₂-10 and sPLA₂-12A

Cytosolic, calcium-dependent forms: cPLA₂-4A, cPLA₂-4B, cPLA₂-4C, cPLA₂-4D, cPLA₂-4E and cPLA₂-4F

Other forms: PLA₂-G5, iPLA₂-G6, PLA₂-G7 and PAFAH2 (platelet-activating factor acetylhydrolase 2)

Nomenclature	sPLA ₂ -1B	sPLA ₂ -2A	sPLA ₂ -2D	sPLA ₂ -2E	sPLA ₂ -2F
HGNC, UniProt	PLA2G1B, P04054	PLA2G2A, P14555	PLA2G2D, Q9UNK4	PLA2G2E, Q9NZK7	PLA2G2F, Q9BZM2

Nomenclature	sPLA ₂ -3	sPLA ₂ -10	sPLA ₂ -12A	cPLA ₂ -4A	cPLA ₂ -4B
HGNC, UniProt	PLA2G3, Q9NZ20	PLA2G10, O15496	PLA2G12A, Q9BZM1	PLA2G4A, P47712	PLA2G4B, P0C869
Comments	–	–	–	cPLA ₂ -4A also expresses lysophospholipase (EC 3.1.1.5) activity [435].	–

Nomenclature	cPLA ₂ -4C	cPLA ₂ -4D	cPLA ₂ -4E	cPLA ₂ -4F
HGNC, UniProt	PLA2G4C, Q9UP65	PLA2G4D, Q86XP0	PLA2G4E, Q3MJ16	PLA2G4F, Q68DD2

Nomenclature	PLA ₂ -G5	iPLA ₂ -G6	PLA ₂ -G7	platelet-activating factor acetylhydrolase 2, 40kDa
HGNC, UniProt	PLA2G5, P39877	PLA2G6, O60733	PLA2G7, Q13093	PAFAH2, Q99487
Inhibitors	–	–	darapladib (pIC ₅₀ 10) [39]	–
Selective inhibitors	–	–	rilapladib (Competitive) (pIC ₅₀ 9.6) [523]	–
Comments	–	–	–	PAFAH2 also expresses PAF hydrolase activity (EC 3.1.1.47)

Comments: The sequence of PLA₂-2C suggests a lack of catalytic activity, while PLA₂-12B (GXIIIB, GXIII sPLA₂-like) appears to be catalytically inactive [413]. A further fragment has been identified with sequence similarities to Group II PLA₂ members. Otoconin 90 (OC90) shows sequence homology to PLA₂-G10.

A binding protein for secretory phospholipase A₂ has been identified which shows modest selectivity for sPLA₂-1B over sPLA₂-2A, and also binds snake toxin phospholipase A₂ [12]. The binding protein appears to have clearance function for circulating secretory phospholipase A₂, as well as signalling functions, and is a

candidate antigen for idiopathic membranous nephropathy [27]. PLA₂-G7 and PAFAH2 also express platelet-activating factor acetylhydrolase activity (EC 3.1.1.47).

Phosphatidylcholine-specific phospholipase D

Enzymes → Glycerophospholipid turnover → Phosphatidylcholine-specific phospholipase D

Overview: Phosphatidylcholine-specific phospholipase D (PLD, EC 3.1.1.4) catalyses the formation of phosphatidic acid from phosphatidylcholine. In addition, the enzyme can make use of alcohols, such as butanol in a transphosphatidyl reaction [399].

Nomenclature	PLD1	PLD2
HGNC, UniProt	PLD1, Q13393	PLD2, O14939
Endogenous activators	ADP-ribosylation factor 1 (ARF1, P84077), PIP ₂ , RhoA, PKC evoked phosphorylation, RalA [189, 303]	–
Endogenous inhibitor	Gβγ [391]	Gβγ [391]
Endogenous activators	–	ADP-ribosylation factor 1 (ARF1, P84077), PIP ₂ [298], oleic acid [418]
Selective inhibitors	–	VU0364739 (pIC ₅₀ 7.7) [279]

Comments: A lysophospholipase D activity (*ENPP2*, [Q13822](#), also known as ectonucleotide pyrophosphatase/phosphodiesterase 2, phosphodiesterase I, nucleotide pyrophosphatase 2, autotaxin) has been described, which not only catalyses the production of lysophosphatidic acid (LPA) from lysophosphatidylcholine, but also cleaves ATP (see Goding *et al.*, 2003 [[175](#)]). Additionally, an N-acylethanolamine-specific phospholipase D (*NAPEPLD*, [Q61Q20](#)) has been char-

acterized, which appears to have a role in the generation of endocannabinoids/endovanilloids, including anandamide [[362](#)]. This enzyme activity appears to be enhanced by polyamines in the physiological range [[292](#)] and fails to transphosphatidylate with alcohols [[381](#)].

Three further, less well-characterised isoforms are PLD3 (*PLD3*, [Q8IV08](#), other names Choline phosphatase 3, HindIII K4L homolog, Hu-K4), PLD4 (*PLD4*, [Q96BZ4](#), other names Choline

phosphatase 4, Phosphatidylcholine-hydrolyzing phospholipase, D4C14orf175 UNQ2488/PRO5775) and PLD5 (*PLD5*, [Q8N7P1](#)). PLD3 has been reported to be involved in myogenesis [[365](#)]. PLD4 is described not to have phospholipase D catalytic activity [[539](#)], but has been associated with inflammatory disorders [[360](#), [468](#), [484](#)]. Sequence analysis suggests that PLD5 is catalytically inactive.

Lipid phosphate phosphatases

Enzymes → Glycerophospholipid turnover → Lipid phosphate phosphatases

Overview: Lipid phosphate phosphatases, divided into phosphatidic acid phosphatases or lipins catalyse the dephosphorylation of phosphatidic acid (and other phosphorylated lipid derivatives) to generate inorganic phosphate and diacylglycerol. PTEN, a phosphatase and tensin homolog (BZS, MHAM, MMAC1, PTEN1, TEP1) is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase which acts as a tumour suppressor by reducing cellular levels of PI 3,4,5-P, thereby toning down activity of PDK1 and PKB. Loss-of-function mutations are frequently identified as somatic mutations in cancers.

Nomenclature	Lipin1	Lipin2	Lipin3	PPA2A	PPA2B	PPA3A	phosphatase and tensin homolog
HGNC, UniProt	<i>LPIN1</i> , Q14693	<i>LPIN2</i> , Q92539	<i>LPIN3</i> , Q9BQK8	<i>PPAP2A</i> , O14494	<i>PPAP2B</i> , O14495	<i>PPAP2C</i> , O43688	<i>PTEN</i> , P60484
EC number	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.4	3.1.3.67 3.1.3.48 3.1.3.16
Substrates	–	phosphatidic acid	–	–	phosphatidic acid	–	phosphatidylinositol (3,4,5)-trisphosphate

Further Reading

- Astudillo AM *et al.* (2012) Dynamics of arachidonic acid mobilization by inflammatory cells. *Biochim. Biophys. Acta* **1821**: 249-56 [[PMID:22155285](#)]
- Berridge MJ. (2009) Inositol trisphosphate and calcium signalling mechanisms. *Biochim. Biophys. Acta* **1793**: 933-40 [[PMID:19010359](#)]
- Brown HA *et al.* (2011) Introduction to lipid biochemistry, metabolism, and signaling. *Chem. Rev.* **111**: 5817-20 [[PMID:21951202](#)]
- Bunney TD *et al.* (2011) PLC regulation: emerging pictures for molecular mechanisms. *Trends Biochem. Sci.* **36**: 88-96 [[PMID:20870410](#)]
- Clayton EL *et al.* (2013) Mammalian phosphatidylinositol 4-kinases as modulators of membrane trafficking and lipid signaling networks. *Prog. Lipid Res.* **52**: 294-304 [[PMID:23608234](#)]
- Dan P *et al.* (2012) Phospholipase A₂ activities in skin physiology and pathology. *Eur. J. Pharmacol.* **691**: 1-8 [[PMID:22819703](#)]
- Harden TK *et al.* (2011) Mechanism of activation and inactivation of Gq/phospholipase C-β signaling nodes. *Chem. Rev.* **111**: 6120-9 [[PMID:21988240](#)]
- Hermansson M *et al.* (2011) Mechanisms of glycerophospholipid homeostasis in mammalian cells. *Prog. Lipid Res.* **50**: 240-57 [[PMID:21382416](#)]

- Hui DY. (2012) Phospholipase A(2) enzymes in metabolic and cardiovascular diseases. *Curr. Opin. Lipidol.* **23**: 235-40 [PMID:22327613]
- Kok BP *et al.* (2012) Unlike two peas in a pod: lipid phosphate phosphatases and phosphatidate phosphatases. *Chem. Rev.* **112**: 5121-46 [PMID:22742522]
- Liu Y *et al.* (2010) Phosphoinositide phosphatases in cell biology and disease. *Prog. Lipid Res.* **49**: 201-17 [PMID:20043944]
- Lyon AM *et al.* (2013) Structural insights into phospholipase C- β function. *Mol. Pharmacol.* **84**: 488-500 [PMID:23880553]
- Quach ND *et al.* (2014) Secretory phospholipase A2 enzymes as pharmacological targets for treatment of disease. *Biochem. Pharmacol.* **90**: 338-48 [PMID:24907600]
- Selvy PE *et al.* (2011) Phospholipase D: enzymology, functionality, and chemical modulation. *Chem. Rev.* **111**: 6064-119 [PMID:21936578]
- Song MS *et al.* (2012) The functions and regulation of the PTEN tumour suppressor. *Nat. Rev. Mol. Cell Biol.* **13**: 283-96 [PMID:22473468]
- Stephens L *et al.* (2013) More paths to PI3K γ . *PLoS Biol.* **11**: e1001594 [PMID:23853549]
- Sánchez-Fernández G *et al.* (2014) G α_q signalling: the new and the old. *Cell. Signal.* **26**: 833-48 [PMID:24440667]
- Woscholski R. (2014) Chemical intervention tools to probe phosphoinositide-dependent signalling. *Biochem. Soc. Trans.* **42**: 1343-8 [PMID:25233413]
- Yagami T *et al.* (2014) The role of secretory phospholipase A₂ in the central nervous system and neurological diseases. *Mol. Neurobiol.* **49**: 863-76 [PMID:24113843]

Haem oxygenase

Enzymes → Haem oxygenase

Overview: Haem oxygenase (heme,hydrogen-donor:oxygen oxidoreductase (α -methene-oxidizing, hydroxylating)), E.C. 1.14.99.3, converts heme into biliverdin and carbon monoxide, utilizing NADPH as cofactor.

Nomenclature	Haem oxygenase 1	Haem oxygenase 2
Common abbreviation	HO1	HO2
HGNC, UniProt	HMOX1, P09601	HMOX2, P30519
EC number	1.14.99.3	1.14.99.3

Comments: The existence of a third non-catalytic version of haem oxygenase, HO3, has been proposed, although this has been suggested to be a pseudogene [202]. The chemical tin protoporphyrin IX acts as a haem oxygenase inhibitor in rat liver with an IC₅₀ value of 11 nM [120].

Further Reading

- Abraham NG *et al.* (2008) Pharmacological and clinical aspects of heme oxygenase. *Pharmacol. Rev.* **60**: 79-127 [PMID:18323402]
- George EM *et al.* (2014) The heme oxygenases: important regulators of pregnancy and preeclampsia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **307**: R769-77 [PMID:24898840]
- Gozzelino R *et al.* (2010) Mechanisms of cell protection by heme oxygenase-1. *Annu. Rev. Pharmacol. Toxicol.* **50**: 323-54 [PMID:20055707]
- Poulos TL. (2014) Heme enzyme structure and function. *Chem. Rev.* **114**: 3919-62 [PMID:24400737]
- Rochette L *et al.* (2013) Carbon monoxide: mechanisms of action and potential clinical implications. *Pharmacol. Ther.* **137**: 133-52 [PMID:23026155]
- Wegiel B *et al.* (2013) The social network of carbon monoxide in medicine. *Trends Mol Med* **19**: 3-11 [PMID:23140858]

Hydrogen sulphide synthesis

Enzymes → Hydrogen sulphide synthesis

Overview: Hydrogen sulfide is a putative gasotransmitter, with similarities to nitric oxide and carbon monoxide. Although the enzymes indicated have multiple enzymatic activities, the focus here is the generation of hydrogen sulphide and the enzymatic characteristics are described accordingly. Cystathionine β -synthase and cystathionine γ -lyase are pyridoxal phosphate-dependent enzymes, while 3-mercaptopyruvate sulfurtransferase functions as a pyridoxal phosphate-independent pathway.

Nomenclature	Cystathionine β -synthase	Cystathionine γ -lyase	L-Cysteine:2-oxoglutarate aminotransferase	3-Mercaptopyruvate sulfurtransferase
Common abbreviation	CBS	CSE	CAT	MPST
HGNC, UniProt	CBS , P35520	CTH , P32929	CCBL1 , Q16773	MPST , P25325
EC number	4.2.1.22	4.4.1.1	4.4.1.13	2.8.1.2
Endogenous substrates	L-cysteine (K_m $6 \times 10^{-3}M$) [74], L-homocysteine	L-cysteine	L-cysteine	3-mercaptopyruvic acid (K_m $1.2 \times 10^{-3}M$) [345]
Products	cystathionine	NH ₃ , pyruvic acid	NH ₃ , pyruvic acid	pyruvic acid
Cofactors	pyridoxal phosphate	pyridoxal phosphate	pyridoxal phosphate	Zn ²⁺
Inhibitors	aminoxyacetic acid	propargylglycine	–	–

Further Reading

Be^atowski J. (2015) Hydrogen sulfide in pharmacology and medicine—An update. *Pharmacol Rep* **67**: 647-58 [[PMID:25933982](#)]
 Li L *et al.* (2011) Hydrogen sulfide and cell signaling. *Annu. Rev. Pharmacol. Toxicol.* **51**: 169-87 [[PMID:21210746](#)]
 Nagy P *et al.* (2014) Chemical aspects of hydrogen sulfide measurements in physiological samples.

Biochim. Biophys. Acta **1840**: 876-91 [[PMID:23769856](#)]
 Wallace JL *et al.* (2015) Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. *Nat Rev Drug Discov* **14**: 329-45 [[PMID:25849904](#)]
 Wang R *et al.* (2015) The role of H₂S bioavailability in endothelial dysfunction. *Trends Pharmacol. Sci.* [[PMID:26071118](#)]

Hydrolases

Enzymes → Hydrolases

Overview: Listed in this section are hydrolases not accumulated in other parts of the Concise Guide, such as monoacylglycerol lipase and acetylcholinesterase. Pancreatic lipase is the predominant mechanism of fat digestion in the alimentary system; its inhibition is associated with decreased fat absorption. CES1 is present at lower levels in the gut than CES2 (P23141), but predominates in the liver, where it is responsible for the hydrolysis of many aliphatic, aromatic and steroid esters. Hormone-sensitive lipase is also a relatively non-selective esterase associated with steroid ester hydrolysis and triglyceride metabolism, particularly in adipose tissue. Endothelial lipase is secreted from endothelial cells and regulates circulating cholesterol in high density lipoproteins.

Nomenclature	pancreatic lipase	lipase, endothelial	carboxylesterase 1	lipase, hormone-sensitive
Common abbreviation	PNLIP	LIPG	CES1	LIPE
HGNC, UniProt	PNLIP , P16233	LIPG , Q9Y5X9	CES1 , P23141	LIPE , Q05469
EC number	3.1.1.3	3.1.1.3	3.1.1.1	3.1.1.79
Inhibitors	orlistat (pIC ₅₀ 8.9) [51]	–	–	–

Further Reading

Markey, G.M. (2011) Carboxylesterase 1 (Ces1): from monocyte marker to major player. *J Clin Pathol* **64**: 107-109 [[PMID:21177752](#)]

Inositol phosphate turnover

Enzymes → Inositol phosphate turnover

Overview: The sugar alcohol *D-myo*-inositol is a component of the [phosphatidylinositol signalling cycle](#), where the principal second messenger is inositol 1,4,5-trisphosphate, IP_3 , which acts at intracellular ligand-gated ion channels, [IP₃ receptors](#) to elevate intracellular calcium. IP_3 is recycled to inositol by phosphatases or phosphorylated to form other active inositol polyphosphates. Inositol produced from dephosphorylation of IP_3 is recycled into membrane phospholipid under the influence of phosphatidylinositol synthase activity (CDP-diacylglycerol-inositol 3-phosphatidyltransferase [[EC 2.7.8.11](#)]).

Inositol 1,4,5-trisphosphate 3-kinases

Enzymes → Inositol phosphate turnover → Inositol 1,4,5-trisphosphate 3-kinases

Overview: Inositol 1,4,5-trisphosphate 3-kinases (E.C. 2.7.1.127, ENSFM00250000001260) catalyse the generation of inositol 1,3,4,5-tetrakisphosphate (IP₄) from IP₃. IP₃ kinase activity is enhanced in the presence of calcium/calmodulin (CALMI CALM2 CALM3, P62158) [91].

Inositol polyphosphate phosphatases

Enzymes → Inositol phosphate turnover → Inositol polyphosphate phosphatases

Overview: Members of this family exhibit phosphatase activity towards IP₃, as well as towards other inositol derivatives, including the phospholipids PIP₂ and PIP₃. With IP₃ as substrate, 1-phosphatase (EC 3.1.3.57) generates 4,5-IP₂, 4-phosphatases (EC 3.1.3.66, ENSFM00250000001432) generate 1,5-IP₂ and 5-phosphatases (E.C. 3.1.3.36 or 3.1.3.56) generate 1,4-IP₂.

Comments: *In vitro* analysis suggested IP₃ and IP₄ were poor substrates for SKIP, synaptojanin 1 and synaptojanin 2, but suggested that PIP₂ and PIP₃ were more efficiently hydrolysed [422].

Inositol monophosphatase

Enzymes → Inositol phosphate turnover → Inositol monophosphatase

Overview: Inositol monophosphatase (E.C. 3.1.3.25, 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. Li⁺ is a nonselective un-competitive inhibitor more potent at IMPase 1 (pK_i ca. 3.5, [324]; pIC₅₀ 3.2, [359]) than IMPase 2 (pIC₅₀ 1.8–2.1, [359]). IMPase activity may be inhibited competitively by L690330 (pK_i 5.5, [324]), although the enzyme selectivity is not yet established.

Nomenclature	IMPase 1	IMPase 2
HGNC, UniProt	IMPA1, P29218	IMPA2, O14732
EC number	3.1.3.25	3.1.3.25
Rank order of affinity	inositol 4-phosphate > inositol 3-phosphate > inositol 1-phosphate [324]	–
Inhibitors	Li ⁺ (pK _i 3.5) [324]	–

Comments: Polymorphisms in either of the genes encoding these enzymes have been linked with bipolar disorder [443, 444, 540]. Disruption of the gene encoding IMPase 1, but not IMPase 2, appears to mimic the effects of Li⁺ in mice [97, 98].

Further Reading

- Barker CJ *et al.* (2013) New horizons in cellular regulation by inositol polyphosphates: insights from the pancreatic β -cell. *Pharmacol. Rev.* **65**: 641-69 [PMID:23429059]
- Billcliff PG *et al.* (2014) Inositol lipid phosphatases in membrane trafficking and human disease. *Biochem. J.* **461**: 159-75 [PMID:24966051]
- Chiu CT *et al.* (2010) Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders. *Pharmacol. Ther.* **128**: 281-304 [PMID:20705090]
- Pirruccello M *et al.* (2012) Inositol 5-phosphatases: insights from the Lowe syndrome protein OCRL. *Trends Biochem. Sci.* **37**: 134-43 [PMID:22381590]
- Schell MJ. (2010) Inositol trisphosphate 3-kinases: focus on immune and neuronal signaling. *Cell. Mol. Life Sci.* **67**: 1755-78 [PMID:20066467]

Lanosterol biosynthesis pathway

Enzymes → Lanosterol biosynthesis pathway

Overview: Lanosterol is a precursor for cholesterol, which is synthesized primarily in the liver in a pathway often described as the mevalonate or HMG-CoA reductase pathway. The first two steps (formation of acetoacetyl CoA and the mitochondrial generation of (S)-3-hydroxy-3-methylglutaryl-CoA) are also associated with oxidation of fatty acids.

Nomenclature	acetyl-CoA acetyltransferase 1, acetyl-CoA acetyltransferase 2	hydroxymethylglutaryl-CoA synthase 1, hydroxymethylglutaryl-CoA synthase 2
HGNC, UniProt	ACAT1, P24752, ACAT2, Q9BWD1	HMGCS1, Q01581, HMGCS2, P54868
EC number	2.3.1.9: 2acetyl CoA = acetoacetyl CoA + coenzyme A	2.3.3.10: acetyl CoA + H ₂ O + acetoacetyl CoA -> (S)-3-hydroxy-3-methylglutaryl-CoA + coenzyme A
Comments	-	HMGCoA synthase is found in cytosolic (HMGCoA synthase 1) and mitochondrial (HMGCoA synthase 2) versions; the former associated with (R)-mevalonate synthesis and the latter with ketogenesis.

Nomenclature	hydroxymethylglutaryl-CoA reductase	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase
HGNC, UniProt	HMGCR, P04035	MVK, Q03426	PMVK, Q15126	MVD, P53602
EC number	1.1.1.34: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> (R)-mevalonate + coenzyme A + NADP ⁺ Reaction mechanism:: First step: (S)-3-hydroxy-3-methylglutaryl-CoA + NADPH -> mevaldyl-CoA + NADP ⁺ Second step: mevaldyl-CoA + H ₂ O -> (R)-mevalonate + NADP ⁺	2.7.1.36: ATP + (R)-mevalonate -> adenosine diphosphate + (R)-5-phosphomevalonate	2.7.4.2: ATP + (R)-5-phosphomevalonate = adenosine diphosphate + (R)-5-diphosphomevalonate	4.1.1.33: ATP + (R)-5-diphosphomevalonate -> adenosine diphosphate + isopentenyl diphosphate + CO ₂ + PO ₃ ⁴⁻

(continued)				
Nomenclature	hydroxymethylglutaryl-CoA reductase	mevalonate kinase	phosphomevalonate kinase	diphosphomevalonate decarboxylase
Inhibitors	lovastatin (Competitive) (pK _i 9.2) [8], rosuvastatin (Competitive) (pIC ₅₀ 8.3) [228], cerivastatin (Competitive) (pK _i 8.2) [61], atorvastatin (Competitive) (pIC ₅₀ 8.1) [228], cerivastatin (Competitive) (pIC ₅₀ 8) [486], simvastatin (Competitive) (pIC ₅₀ 8) [228], fluvastatin (Competitive) (pIC ₅₀ 7.6) [228]	–	–	–
Comments	HMGCoA reductase is associated with intracellular membranes; enzymatic activity is inhibited by phosphorylation by AMP-activated kinase. The enzymatic reaction is a three-step reaction involving the intermediate generation of mevaldehyde-CoA and mevaldehyde.	Mevalonate kinase activity is regulated by the downstream products farnesyl diphosphate and geranyl diphosphate as an example of feedback inhibition.	–	–

Nomenclature	isopentenyl-diphosphate Δ-isomerase 1	isopentenyl-diphosphate Δ-isomerase 1	geranylgeranyl diphosphate synthase	farnesyl diphosphate synthase
HGNC, UniProt	<i>ID11</i> , Q13907	<i>ID12</i> , Q9BXS1	<i>GGPS1</i> , O95749	<i>FDPS</i> , P14324
EC number	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	5.3.3.2: isopentenyl diphosphate = dimethylallyl diphosphate	2.5.1.29: trans,trans-farnesyl diphosphate + isopentenyl diphosphate -> geranylgeranyl diphosphate + diphosphate 2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate	2.5.1.10: geranyl diphosphate + isopentenyl diphosphate -> trans,trans-farnesyl diphosphate + diphosphate 2.5.1.1: dimethylallyl diphosphate + isopentenyl diphosphate = geranyl diphosphate + diphosphate
Inhibitors	–	–	–	risedronate (pIC ₅₀ 8.4) [31], zoledronic acid (pK _i 7.1) [121], alendronate (pIC ₅₀ 6.3) [31]
Selective inhibitors	–	–	–	ibandronic acid (pK _i 6.7) [121], pamidronic acid (pIC ₅₀ 6.7) [121]

Nomenclature	squalene synthase	squalene monooxygenase	lanosterol synthase
HGNC, UniProt	FDFT1 , P37268	SQLE , Q14534	LSS , P48449
EC number	2.5.1.21 : 2trans,trans-farnesyl diphosphate -> presqualene diphosphate + diphosphate presqualene diphosphate + NAD(P)H + H ⁺ -> squalene + diphosphate + NAD(P) ⁺	1.14.13.132 : H ⁺ + NADPH + O ₂ + squalene = H ₂ O + NADP ⁺ + (S)-2,3-epoxysqualene	5.4.99.7 : (S)-2,3-epoxysqualene = lanosterol
Cofactors	NADPH	–	–
Inhibitors	zaragozic acid A (pK _i 10.1) [32] – Rat, zaragozic acid A (pIC ₅₀ 9.2) [488]	–	–

Further Reading

- Miziorko HM. (2011) Enzymes of the mevalonate pathway of isoprenoid biosynthesis. *Arch. Biochem. Biophys.* **505**: 131-43 [[PMID:20932952](#)]
- Rozman D *et al.* (2010) Perspectives of the non-statin hypolipidemic agents. *Pharmacol. Ther.* **127**: 19-40 [[PMID:20420853](#)]
- Seiki S *et al.* (2009) Pharmacologic inhibition of squalene synthase and other downstream enzymes of the cholesterol synthesis pathway: a new therapeutic approach to treatment of hypercholesterolemia. *Cardiol Rev* **17**: 70-6 [[PMID:19367148](#)]
- Zhang H *et al.* (2014) Cholesterol and lipoprotein metabolism: Early Career Committee contribution. *Arterioscler. Thromb. Vasc. Biol.* **34**: 1791-4 [[PMID:25142876](#)]
- van der Burgh R *et al.* (2012) Mevalonate kinase deficiency, a metabolic autoinflammatory disease. *Clin. Immunol.* [[PMID:23110805](#)]

Nucleoside synthesis and metabolism

Enzymes → [Nucleoside synthesis and metabolism](#)

Overview: The *de novo* synthesis and salvage of nucleosides have been targeted for therapeutic advantage in the treatment of particular cancers and gout. Dihydrofolate reductase produces tetrahydrofolate, a cofactor required for synthesis of purines, pyrimidines and amino acids. GART allows formylation of phosphoribosylglycinamide, an early step in purine biosynthesis. Dihydroorotate dehydrogenase produces orotate, a key intermediate in pyrimidine synthesis. IMP dehydrogenase generates xanthosine monophosphate, an intermediate in GTP synthesis.

Nomenclature	dihydrofolate reductase	dihydroorotate dehydrogenase (quinone)	IMP (inosine 5'-monophosphate) dehydrogenase 1	IMP (inosine 5'-monophosphate) dehydrogenase 2
HGNC, UniProt	DHFR , P00374	DHODH , Q02127	IMPDH1 , P20839	IMPDH2 , P12268
EC number	1.5.1.3	1.3.5.2	1.1.1.205	1.1.1.205

(continued)				
Nomenclature	dihydrofolate reductase	dihydroorotate dehydrogenase (quinone)	IMP (inosine 5'-monophosphate) dehydrogenase 1	IMP (inosine 5'-monophosphate) dehydrogenase 2
Inhibitors	pemetrexed (p <i>K</i> _i 8.1) [161, 436], pralatrexate (p <i>K</i> _i 7.3) [231]	teriflunomide (p <i>K</i> _i 7.5) [204], leflunomide (p <i>K</i> _i 4.9) [372]	mycophenolic acid (p <i>I</i> C ₅₀ 7.7) [351], ribavirin (p <i>I</i> C ₅₀ 5.6–6) [526], mycophenolate mofetil, thioguanine [124, 502]	mycophenolic acid (p <i>I</i> C ₅₀ 7.7) [351], ribavirin (p <i>I</i> C ₅₀ 5.6–6) [526], mycophenolate mofetil (See Inhibitor Comment below), thioguanine [124, 502]
Selective inhibitors	methotrexate (p <i>K</i> _i 8.9) [412]	–	–	–

Nomenclature	xanthine dehydrogenase	ribonucleotide reductase M1	ribonucleotide reductase M2	ribonucleotide reductase M2 B (TP53 inducible)
HGNC, UniProt	<i>XDH</i> , P47989	<i>RRM1</i> , P23921	<i>RRM2</i> , P31350	<i>RRM2B</i> , Q7LG56
EC number	1.1.7.1.4	1.17.14.1	1.17.4.1	1.17.1.4
Inhibitors	febuxostat (p <i>K</i> _i 9.9) [361] – Bovine, febuxostat (p <i>I</i> C ₅₀ 7.5) [255] – Bovine, allopurinol (p <i>I</i> C ₅₀ 5.4) [34], allopurinol (p <i>K</i> _i 5.2) [34]	clofarabine (p <i>I</i> C ₅₀ 8.3) [375], fludarabine (p <i>I</i> C ₅₀ 6) [491], hydroxyurea (p <i>I</i> C ₅₀ 3.8) [433], gemcitabine [205]	clofarabine (p <i>I</i> C ₅₀ 8.3) [375], fludarabine (p <i>I</i> C ₅₀ 6) [491], hydroxyurea (p <i>I</i> C ₅₀ 3.8) [433], gemcitabine [205]	–

Nomenclature	thymidylate synthetase	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	purine nucleoside phosphorylase
Common abbreviation	–	GART	–
HGNC, UniProt	<i>TYMS</i> , P04818	<i>GART</i> , P22102	<i>PNP</i> , P00491
EC number	2.1.1.45	2.1.2.2 6.3.3.1 6.3.4.13	–

(continued)			
Nomenclature	thymidylate synthetase	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	purine nucleoside phosphorylase
Inhibitors	pemetrexed (p <i>K</i> _i 7) [436], capecitabine [63, 373]	pemetrexed (p <i>K</i> _i 5) [436] – Mouse	–
Selective inhibitors	raltitrexed (p <i>C</i> ₅₀ 6.5) [162]	–	–

Comments: Thymidylate synthetase allows the interconversion of dUMP and dTMP, thereby acting as a crucial step in DNA synthesis. Purine nucleoside phosphorylase allows separation of a nucleoside into the nucleobase and ribose phosphate for nucleotide salvage. Xanthine dehydrogenase generates urate in the purine degradation pathway. Post-translational modifications of xanthine dehydrogenase convert the enzymatic reaction to a xanthine oxidase, allowing the interconversion of hypoxanthine and xanthine, with the production (or consumption) of reactive oxygen species. Ribonucleotide reductases allow the production of deoxyribonucleotides from ribonucleotides.

Further Reading

- Battelli MG *et al.* (2014) Pathophysiology of circulating xanthine oxidoreductase: new emerging roles for a multi-tasking enzyme. *Biochim. Biophys. Acta* **1842**: 1502-17 [PMID:24882753]
- Cantu-Medellin N *et al.* (2013) Xanthine oxidoreductase-catalyzed reduction of nitrite to nitric oxide: insights regarding where, when and how. *Nitric Oxide* **34**: 19-26 [PMID:23454592]
- Glander P *et al.* (2012) Inosine 5'-monophosphate dehydrogenase activity as a biomarker in the field of transplantation. *Clin. Chim. Acta* **413**: 1391-7 [PMID:21889500]
- Munier-Lehmann H *et al.* (2013) On dihydroorotate dehydrogenases and their inhibitors and uses. *J. Med. Chem.* **56**: 3148-67 [PMID:23452331]

Sphingosine 1-phosphate turnover

Enzymes → Sphingosine 1-phosphate turnover

Overview: S1P (sphingosine 1-phosphate) is a pro-survival signal, in contrast to ceramide. It is formed by the sphingosine kinase-catalysed phosphorylation of sphingosine. S1P can be released from cells to act as an agonist at a family of five G protein-coupled receptors (S1P₁₋₅) but also has intracellular targets. S1P can be dephosphorylated back to sphingosine or hydrolysed to form hexadecanal and phosphoethanolamine. Sphingosine choline phosphotransferase (EC 2.7.8.10) generates sphingylphosphocholine from sphingosine and CDP-choline. Sphingosine β-galactosyltransferase (EC 2.4.1.23) generates psychosine from sphingosine in the presence of UDP-α-D-galactose. The molecular identities of these enzymes have not been confirmed.

Further Reading

- Chan H *et al.* (2013) Post-translational regulation of sphingosine kinases. *Biochim. Biophys. Acta* **1831**: 147-56 [PMID:22801036]
- Khavandgar Z *et al.* (2015) Sphingolipid metabolism and its role in the skeletal tissues. *Cell. Mol. Life Sci.* **72**: 959-69 [PMID:25424644]
- Maceyka M *et al.* (2014) Sphingolipid metabolites in inflammatory disease. *Nature* **510**: 58-67 [PMID:24899305]
- Plano D *et al.* (2014) Importance of sphingosine kinase (SphK) as a target in developing cancer therapeutics and recent developments in the synthesis of novel SphK inhibitors. *J. Med. Chem.* **57**: 5509-24 [PMID:24471412]
- Pyne S *et al.* (2011) Translational aspects of sphingosine 1-phosphate biology. *Trends Mol Med* **17**: 463-72 [PMID:21514226]
- Rosen H *et al.* (2013) Sphingosine-1-phosphate and its receptors: structure, signaling, and influence. *Annu. Rev. Biochem.* **82**: 637-62 [PMID:23527695]
- Schwalm S *et al.* (2014) Targeting the sphingosine kinase/sphingosine 1-phosphate pathway to treat chronic inflammatory kidney diseases. *Basic Clin. Pharmacol. Toxicol.* **114**: 44-9 [PMID:23789924]

Sphingosine kinase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine kinase

Nomenclature	sphingosine kinase 1 sphingosine kinase 2
Common abbreviation	SPHK1, SPHK2
HGNC, UniProt	<i>SPHK1</i> , <i>Q9NYA1</i> <i>SPHK2</i> , <i>Q9NRA0</i>
EC number	2.7.1.91: sphingosine + ATP = sphingosine 1-phosphate + adenosine diphosphate ATP + sphinganine = sphinganine 1-phosphate + adenosine diphosphate
Cofactors	Mg ²⁺ [432]
Inhibitors	PF-543 (pIC ₅₀ 8.7) [425], SK1-I [377], ABC294640 [148], ROME [287]
(Sub)family-selective inhibitors	sphingosine kinase inhibitor (pIC ₅₀ 6.3) [147]

Further Reading

Neubauer HA *et al.* (2013) Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS J.* **280**: 5317-36 [PMID:23638983] Truman JP *et al.* (2014) Evolving concepts in cancer therapy through targeting sphingolipid metabolism. *Biochim. Biophys. Acta* **1841**: 1174-88 [PMID:24384461]

Sphingosine 1-phosphate phosphatase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 1-phosphate phosphatase

Nomenclature	sphingosine-1-phosphate phosphatase 1	sphingosine-1-phosphate phosphatase 2
Common abbreviation	SGPP1	SGPP2
HGNC, UniProt	<i>SGPP1</i> , <i>Q9BX95</i>	<i>SGPP2</i> , <i>Q8IWX5</i>
EC number	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate	3.1.3.-: sphingosine 1-phosphate -> sphingosine + inorganic phosphate
Comments	Depletion of S1P phosphohydrolase-1 (SPP1), which degrades intracellular S1P, induces the unfolded protein response and endoplasmic reticulum stress-induced autophagy [307].	–

Sphingosine 1-phosphate lyase

Enzymes → Sphingosine 1-phosphate turnover → Sphingosine 1-phosphate lyase

Nomenclature	sphingosine-1-phosphate lyase 1
HGNC, UniProt	SGPL1 , O95470
EC number	4.1.2.27: sphingosine 1-phosphate -> phosphoethanolamine + hexadecanal
Cofactors	pyridoxal phosphate
Inhibitors	compound 31 [PMID: 24809814] (pIC ₅₀ 6.7) [519]
Comments	THI (2-Acetyl-5-tetrahydroxybutyl imidazole) inhibits the enzyme activity in intact cell preparations [426].

Further Reading

Bigaud M *et al.* (2014) Second generation S1P pathway modulators: research strategies and clinical developments. *Biochim. Biophys. Acta* **1841**: 745-58 [PMID:24239768]
Van Veldhoven PP *et al.* (2000) Human sphingosine-1-phosphate lyase: cDNA cloning, functional

expression studies and mapping to chromosome 10q22(1). *Biochim. Biophys. Acta* **1487**: 128-34 [PMID:11018465]

Thyroid hormone turnover

Enzymes → Thyroid hormone turnover

Overview:

The thyroid hormones triiodothyronine and thyroxine, usually abbreviated as [triiodothyronine](#) and T_4 , respectively, are synthesized in the thyroid gland by sequential metabolism of tyrosine residues in the glycosylated homodimeric protein thyroglobulin ([TG](#), [P01266](#)) under the influence of the haem-containing protein iodide peroxidase. Iodide peroxidase/TPO is a haem-containing

enzyme, from the same structural family as eosinophil peroxidase ([EPX](#), [P11678](#)), lactoperoxidase ([LPO](#), [P22079](#)) and myeloperoxidase ([MPO](#), [P05164](#)). Circulating thyroid hormone is bound to thyroxine-binding globulin ([SERPINA7](#), [P05543](#)).

Tissue deiodinases

These are 1 TM selenoproteins that remove an iodine from T_4 (3,3',5,5'-tetraiodothyronine) to generate [triiodothyronine](#)

(3,3',5-triiodothyronine, a more potent agonist at thyroid hormone receptors) or rT_3 (rT_3 , 3,3',5'-triiodothyronine, a relatively inactive analogue). DIO1 is also able to deiodinate rT_3 to form 3,3'-diiodothyronine (T_2). Iodotyrosine deiodinase is a 1TM homodimeric enzyme.

Nomenclature	thyroid peroxidase	deiodinase, iodothyronine, type I	deiodinase, iodothyronine, type II	deiodinase, iodothyronine, type III	iodotyrosine deiodinase
Common abbreviation	TPO	DIO1	DIO2	DIO3	IYD
HGNC, UniProt	<i>TPO</i> , P07202	<i>DIO1</i> , P49895	<i>DIO2</i> , Q92813	<i>DIO3</i> , P55073	<i>IYD</i> , Q6PHW0
EC number	1.11.1.8: [Thyroglobulin]-L-tyrosine + H ₂ O ₂ + H ⁺ + I ⁻ -> [Thyroglobulin]-3,5,3'- triiodo-L-thyronine + [thyroglobulin]-aminoacrylate + H ₂ O	1.97.1.10: T ₄ -> triiodothyronine rT ₃ -> T ₂	1.97.1.10: T ₄ -> triiodothyronine rT ₃ -> T ₂	1.97.1.11: T ₄ -> triiodothyronine rT ₃ -> T ₂	1.22.1.1: 3-iodotyrosine -> L-tyrosine + I ⁻ 3,5-diiodo-L-tyrosine -> 3-iodotyrosine + I ⁻
Cofactors	Ca ²⁺	-	-	-	flavin adenine dinucleotide, NADPH
Inhibitors	methimazole [349], propylthiouracil [349]	-	-	-	-
Comments	Carbimazole is a pro-drug for methimazole	-	-	-	-

Further Reading

- Arrojo E Drigo R *et al.* (2013) Role of the type 2 iodothyronine deiodinase (D2) in the control of thyroid hormone signaling. *Biochim. Biophys. Acta* **1830**: 3956-64 [PMID:22967761]
- Darras VM *et al.* (2015) Intracellular thyroid hormone metabolism as a local regulator of nuclear thyroid hormone receptor-mediated impact on vertebrate development. *Biochim. Biophys. Acta* **1849**: 130-41 [PMID:24844179]
- Darras VM *et al.* (2012) Iodothyronine deiodinase structure and function: from ascidians to humans. *J. Endocrinol.* **215**: 189-206 [PMID:22825922]
- Gereben B *et al.* (2008) Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. *Endocr. Rev.* **29**: 898-938 [PMID:18815314]
- Waung JA *et al.* (2012) Thyroid hormone metabolism in skeletal development and adult bone maintenance. *Trends Endocrinol. Metab.* **23**: 155-62 [PMID:22169753]

1.14.11.29 2-oxoglutarate oxygenases

Enzymes → 1.14.11.29 2-oxoglutarate oxygenases

Overview: The hypoxia inducible factor (HIF) is a transcriptional complex that is involved in oxygen homeostasis [429]. At normal oxygen levels, the alpha subunit of HIF (HIF-1 α) is targeted for degradation by prolyl hydroxylation by the PHD proteins 1-3 (HIF-PHs) which are 2-oxoglutarate (2OG) oxygenases responsible for the post-translational modification of a specific proline in each of the oxygen-dependent degradation (ODD) domains of HIF-1 α .

Hydroxylated HIFs are then targeted for proteasomal degradation via the von Hippel-Lindau ubiquitination complex [232]. Under hypoxic conditions, the hydroxylation reaction is blunted which results in decreased HIF degradation. The surviving HIFs are then available to translocate to the nucleus where they heterodimerize with HIF-1 β , effecting increased expression of hypoxia-inducible genes.

HIF-PH enzymes are being investigated as pharmacological targets as their inhibition mimics the hypoxic state and switches on transcription of genes associated with processes such as erythropoiesis and vasculogenesis [142]. Small molecule HIF-PH inhibitors are in clinical trial as novel therapies for the amelioration of anemia associated with chronic kidney disease [46].

Nomenclature	egl-9 family hypoxia-inducible factor 2	egl-9 family hypoxia-inducible factor 1	egl-9 family hypoxia-inducible factor 3
Common abbreviation	PHD1	PHD2	PHD3
HGNC, UniProt	EGLN2, Q96KS0	EGLN1, Q9GZT9	EGLN3, Q9H6Z9
EC number	–	1.14.11.29	1.14.11.29
Inhibitors	–	IOX2 (pIC ₅₀ 7.7) [84]	–

2.4.2.30 poly(ADP-ribose)polymerases

Enzymes → 2.4.2.30 poly(ADP-ribose)polymerases

Overview: The Poly ADP-ribose polymerase family is a series of enzymes, where the best characterised members are nuclear proteins which are thought to function by binding to single strand breaks in DNA, allowing the recruitment of repair enzymes by the synthesis of NAD-derived ADP-ribose polymers, which are subsequently degraded by a glycohydrolase ([PARG, Q86W56](#)).

Nomenclature	poly (ADP-ribose) polymerase 1	poly (ADP-ribose) polymerase 2	poly (ADP-ribose) polymerase 3
Common abbreviation	PARP1	PARP2	PARP3
HGNC, UniProt	PARP1, P09874	PARP2, Q9UGN5	PARP3, Q9Y6F1
EC number	2.4.2.30	2.4.2.30	–
Selective inhibitors	AG14361 (pK _i 8.2) [445]	–	–

Further Reading

- Bürkle A *et al.* (2013) Poly(ADP-ribose): PARadigms and PARadoxes. *Mol. Aspects Med.* **34**: 1046-65 [PMID:23290998]
- De Vos M *et al.* (2012) The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. *Biochem. Pharmacol.* **84**: 137-46 [PMID:22469522]
- Lord CJ *et al.* (2012) The DNA damage response and cancer therapy. *Nature* **481**: 287-94 [PMID:22258607]
- Sonnenblick A *et al.* (2015) An update on PARP inhibitors—moving to the adjuvant setting. *Nat Rev Clin Oncol* **12**: 27-41 [PMID:25286972]

2.5.1.58 Protein farnesyltransferase

Enzymes → 2.5.1.58 Protein farnesyltransferase

Overview: Farnesyltransferase is a member of the prenyltransferases family which also includes geranylgeranyltransferase types I (EC 2.5.1.59) and II (EC 2.5.1.60) [66]. Protein farnesyltransferase catalyses the post-translational formation of a thioether linkage between the C-1 of an isoprenyl group and a cysteine residue fourth from the C-terminus of a protein (*ie* to the CaaX motif, where 'a' is an aliphatic amino acid and 'X' is usually serine, me-

thionine, alanine or glutamine; leucine for EC 2.5.1.59) [156]. Farnesyltransferase is a dimer, composed of an alpha and beta subunit and requires Mg²⁺ and Zn²⁺ ions as cofactors. The active site is located between the subunits. Prenylation creates a hydrophobic domain on protein tails which acts as a membrane anchor. Substrates of the prenyltransferases include Ras, Rho, Rab, other

Ras-related small GTP-binding proteins, G-protein γ -subunits, nuclear lamins, centromeric proteins and many proteins involved in visual signal transduction.

In relation to the causative association between oncogenic Ras proteins and cancer, farnesyltransferase has become an important mechanistic drug discovery target.

3.5.3.15 Peptidyl arginine deiminases (PADI)

Enzymes → 3.5.3.15 Peptidyl arginine deiminases (PADI)

Overview: In humans, the peptidyl arginine deiminases (PADIs; [HGNC family link](#)) are a family of five enzymes, PADI1-4 and PADI6. PADIs catalyze the deimination of protein L-arginine residues to L-citrulline and ammonia. The human isozymes exhibit tissue-specific expression patterns [244].

RAS subfamily

Enzymes → 3.6.5.2 Small monomeric GTPases → RAS subfamily

Overview: The RAS proteins (HRAS, NRAS and KRAS) are small membrane-localised G protein-like molecules of 21 kd. They act as an on/off switch linking receptor and non-receptor tyrosine kinase activation to downstream cytoplasmic or nuclear events. Binding of GTP activates the switch, and hydrolysis of the GTP to GDP

inactivates the switch.

The RAS proto-oncogenes are the most frequently mutated class of proteins in human cancers. Common mutations compromise the GTP-hydrolysing ability of the proteins causing constitutive activation [457], which leads to increased cell proliferation and

decreased apoptosis [550]. Because of their importance in oncogenic transformation these proteins have become the targets of intense drug discovery effort [23].

4.2.1.1 Carbonate dehydratases

Enzymes → 4.2.1.1 Carbonate dehydratases

Overview: Carbonic anhydrases facilitate the interconversion of water and carbon dioxide with bicarbonate ions and protons (EC 4.2.1.1), with over a dozen gene products identified in man. The enzymes function in acid-base balance and the movement of carbon dioxide and water. They are targeted for therapeutic gain by particular antiglaucoma agents and diuretics.

Nomenclature	carbonic anhydrase I	carbonic anhydrase VII	carbonic anhydrase XII
HGNC, UniProt	CA1, P00915	CA7, P43166	CA12, O43570
EC number	4.2.1.1	4.2.1.1	4.2.1.1
Inhibitors	chlorthalidone (p <i>K</i> _i 6.5)	methazolamide (p <i>K</i> _i 8.7) [430], acetazolamide (p <i>K</i> _i 8.6) [18], brinzolamide (p <i>K</i> _i 8.6) [430], chlorthalidone (p <i>K</i> _i 8.6) [482]	chlorthalidone (p <i>K</i> _i 8.4) [482], diclofenamide (p <i>K</i> _i 7.3) [504]

Further Reading

- Alterio V *et al.* (2012) Multiple binding modes of inhibitors to carbonic anhydrases: how to design specific drugs targeting 15 different isoforms? *Chem. Rev.* **112**: 4421-68 [PMID:22607219]
- Cummins EP *et al.* (2014) Carbon dioxide-sensing in organisms and its implications for human disease. *Cell. Mol. Life Sci.* **71**: 831-45 [PMID:24045706]
- Imtaiyaz Hassan M *et al.* (2013) Structure, function and applications of carbonic anhydrase isozymes. *Bioorg. Med. Chem.* **21**: 1570-82 [PMID:22607884]
- Sjöblom M. (2011) Duodenal epithelial sensing of luminal acid: role of carbonic anhydrases. *Acta Physiol (Oxf)* **201**: 85-95 [PMID:20632999]

5.99.1.2 DNA Topoisomerases

Enzymes → 5.99.1.2 DNA Topoisomerases

Overview: DNA topoisomerases regulate the supercoiling of nuclear DNA to influence the capacity for replication or transcription. The enzymatic function of this series of enzymes involves cutting the DNA to allow unwinding, followed by re-attachment to reseal the backbone. Members of the family are targeted in anti-cancer chemotherapy.

Nomenclature	topoisomerase (DNA) I	topoisomerase (DNA) II alpha 170kDa
HGNC, UniProt	TOP1, P11387	TOP2A, P11388
EC number	5.99.1.2	5.99.1.2
Inhibitors	irinotecan [117, 477] – Bovine	etoposide (p <i>C</i> ₅₀ 7.3), teniposide [119] – Mouse

Further Reading

- Castelli S *et al.* (2012) Interaction between natural compounds and human topoisomerase I. *Biol. Chem.* **393**: 1327-40 [PMID:23109546]
- Chen SH *et al.* (2013) New mechanistic and functional insights into DNA topoisomerases. *Annu. Rev. Biochem.* **82**: 139-70 [PMID:23495937]
- Kathiravan MK *et al.* (2013) Topoisomerase as target for antibacterial and anticancer drug discovery. *J Enzyme Inhib Med Chem* **28**: 419-35 [PMID:22380774]
- Tomicic MT *et al.* (2013) Topoisomerase degradation, DSB repair, p53 and IAPs in cancer cell resistance to camptothecin-like topoisomerase I inhibitors. *Biochim. Biophys. Acta* **1835**: 11-27 [PMID:23006513]

References

1. Abita JP *et al.* (1976) [182695]
2. Adam-Klages S *et al.* (1996) [8808629]
3. Agarwal RP *et al.* (1977) [849330]
4. Ahn K *et al.* (2007) [17949010]
5. Ahn K *et al.* (2009) [19389627]
6. Ahn K *et al.* (2010) [21115843]
7. Alaamery MA *et al.* (2010) [20228279]
8. Alberts AW *et al.* (1980) [6933445]
9. Alexander SP *et al.* (2007) [17876303]
10. Alger BE *et al.* (2011) [21507493]
11. Almahariq M *et al.* (2013) [23066090]
12. Ancian P *et al.* (1995) [7548076]
13. Aoki M *et al.* (2000) [10991987]
14. Apsel B *et al.* (2008) [18849971]
15. Aritake K *et al.* (2006) [16547010]
16. AstraZeneca. AZ12971554. Accessed on 12/09/2014. astrazeneca.com.
17. Auerbach SS *et al.* National Toxicology Program: Dept of Health and Human Services. Accessed on 02/05/2014. DrugMatrix.
18. Avvaru BS *et al.* (2010) [20605094]
19. Babbedge RC *et al.* (1993) [7693279]
20. Bae YS *et al.* (1998) [9468499]
21. Bae YS *et al.* (2003) [12695532]
22. Baggio R *et al.* (1999) [10454520]
23. Baines AT *et al.* (2011) [22004085]
24. Baylin SB *et al.* (2011) [21941284]
25. Bayly CI *et al.* (1999) [10091674]
26. Beauchamp E *et al.* (2009) [19647031]
27. Beck LH *et al.* (2009) [19571279]
28. Bellier JP *et al.* (2011) [21382474]
29. Berg S *et al.* (2012) [22489897]
30. Bergamini G *et al.* (2012) [22544264]
31. Bergstrom JD *et al.* (2000) [10620343]
32. Bergstrom JD *et al.* (1993) [8419946]
33. Bhatnagar AS *et al.* (1990) [2149502]
34. Biagi G *et al.* (1996) [8691450]
35. Binda C *et al.* (2004) [15027868]
36. Binda C *et al.* (2008) [18426226]
37. Bisogno T *et al.* (2003) [14610053]
38. Black WC *et al.* (2003) [12643942]
39. Blackie JA *et al.* (2003) [12643913]
40. Bland-Ward PA *et al.* (1995) [7544863]
41. Blankman JL *et al.* (2007) [18096503]
42. Blobaum AL *et al.* (2007) [17341061]
43. Blobaum AL *et al.* (2007) [17434872]
44. Boess FG *et al.* (2004) [15555642]
45. Bosanac T *et al.* (2010) [20471253]
46. Bouchie A. (2013) [24213751]
47. Boyle CD *et al.* (2005) [15837326]
48. Buck J *et al.* (1999) [9874775]
49. Burger MT *et al.* (2011) [24900266]
50. Burger RM *et al.* (1975) [1169962]
51. Bustanji Y *et al.* (2010) Inhibition of hormone sensitive lipase and pancreatic lipase by *Rosmarinus officinalis* extract and selected phenolic constituents. *Journal of Medicinal Plants Research* **4**: 2235-2242
52. Butini S *et al.* (2008) [18479118]
53. Butters TD *et al.* (2000) *Tetrahedron: Asymmetry* **11**: 113-124
54. Bylund J *et al.* (2000) [10791960]
55. Bézière N *et al.* (2008) [18667313]
56. Cabaye A *et al.* (2015) [25974248]
57. Cali JJ *et al.* (1994) [8163524]
58. Campbell PJ *et al.* (2006) [17151367]
59. Camps M *et al.* (1992) [1465133]
60. Cano C *et al.* (2013) [23855836]
61. Carbonell T *et al.* (2005) [16128575]
62. Cardozo MG *et al.* (1992) [1738151]
63. Carlini LE *et al.* (2005) [15709193]
64. Carlson BA *et al.* (1996) [8674031]
65. Carozzi A *et al.* (1993) [8380773]
66. Casey PJ *et al.* (1996) [8621375]
67. Ceconi C *et al.* (2007) [17716647]
68. Ceyhan O *et al.* (2012) [22284362]
69. Chadli A *et al.* (2000) [11050175]
70. Chalfant CE *et al.* (1996) [9121494]
71. Chambers KJ *et al.* (1998) [9751809]
72. Chen H *et al.* (2013) [23286832]
73. Chen J *et al.* (1993) [8389756]
74. Chen X *et al.* (2004) [15520012]
75. Chen Y *et al.* (2000) [10915626]
76. Chen Y *et al.* (1997) [9391159]
77. Chen YT *et al.* (2011) *Med Chem Commun* **2**: 73-75
78. Cheng JB *et al.* (2003) [12867411]
79. Chevillard C *et al.* (1994) [7527095]
80. Chin PC *et al.* (2004) [15255937]
81. Choi EJ *et al.* (1992) [1633161]
82. Choudhary C *et al.* (2009) [19608861]
83. Chowdhury MA *et al.* (2009) [19884005]
84. Chowdhury R *et al.* (2013) [23683440]
85. Christiansen JS. (1985) [2951074]
86. Ciechanover A. (2005) [16142822]
87. Clark JK *et al.* (2002) [12182861]
88. Coghlan MP *et al.* (2000) [11033082]
89. Coleman CS *et al.* (2004) [14763899]
90. Colleluori DM *et al.* (2001) [11478904]
91. Conigrave AD *et al.* (1989) [2559811]
92. Corbett JA *et al.* (1992) [1378415]
93. Corbin JD *et al.* (2000) [10785399]
94. Cortés A *et al.* (2015) [24933472]
95. Covey DF *et al.* (1982) [7083195]
96. Crocetti L *et al.* (2011) [21741848]
97. Cryns K *et al.* (2007) [16841073]
98. Cryns K *et al.* (2008) [17460611]
99. Cully M. (2013) [24145894]
100. Curet O *et al.* (1998) [10333983]
101. Daidone F *et al.* (2012) [22384042]
102. Daubner SC *et al.* (2011) [21176768]
103. Davies SP *et al.* (2000) [10998351]
104. Davis JA *et al.* (2010) [20927248]
105. Davis MI *et al.* (2011) [22037378]
106. DeForrest JM *et al.* (1989) [2481187]
107. DePinto W *et al.* (2006) [17121911]
108. Deinum J *et al.* (2009) [19492147]
109. Delhommeau F *et al.* (2006) [17131059]
110. Desai B *et al.* (2013) [23441572]
111. Dewji NN *et al.* (2015) [25923432]
112. Di Paolo JA *et al.* (2011) [21113169]
113. Di Santo R *et al.* (2005) [15974574]
114. DiMauro EF *et al.* (2007) [17280833]
115. Ding Q *et al.* (2006) Diaminotiazoles having antiproliferative activity. Patent number: US7094896. Assignee: Hoffmann-La Roche Inc.. Priority date: 22/12/2001. Publication date: 22/08/2006.
116. Dixon RA *et al.* (1990) [2300173]
117. Dodds HM *et al.* (1998) [9655905]
118. Doe C *et al.* (2007) [17018693]
119. Drake FH *et al.* (1989) [2557897]
120. Drummond GS *et al.* (1981) [6947237]
121. Dunford JE *et al.* (2008) [18327899]
122. Eckhardt M *et al.* (2007) [18052023]
123. Edmondson SD *et al.* (2003) [14592490]
124. Elgmeier GH. (2003) [14529546]
125. Engler TA *et al.* (2004) [15267232]
126. Enserink JM *et al.* (2002) [12402047]

127. Erba F *et al.* (2001) [11172730]
 128. Escalpez M *et al.* (1994) [8126575]
 129. Esteller M. (2008) [18337604]
 130. Fabrias G *et al.* (2012) [125200621]
 131. Faraci WS *et al.* (1996) [8937711]
 132. Faul MM *et al.* (2003) [12749884]
 133. Fawcett L *et al.* (2000) [10725373]
 134. Feelisch M *et al.* (1999) [10419542]
 135. Fer M *et al.* (2008) [18577768]
 136. Fischer L *et al.* (2004) [15197110]
 137. Fisher DA *et al.* (1998) [9624146]
 138. Fisher DA *et al.* (1998) [9618252]
 139. Fitzgerald K *et al.* (2014) [24094767]
 140. Flockhart DA.. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). Accessed on 18/11/2014. <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/>.
 141. Folkes AJ *et al.* (2008) [18754654]
 142. Forristal CE *et al.* (2014) [24371328]
 143. Forsyth T *et al.* (2012) [23127890]
 144. Foss FM *et al.* (2011) [21493798]
 145. Fowler CJ. (2007) [17618306]
 146. Frank-Kamenetsky M *et al.* (2008) [18695239]
 147. French KJ *et al.* (2003) [14522923]
 148. French KJ *et al.* (2010) [20061445]
 149. Friebe A *et al.* (1998) [9855623]
 150. Friebe A *et al.* (1996) [9003762]
 151. Fry DW *et al.* (2004) [15542782]
 152. Fujishige K *et al.* (1999) [10373451]
 153. Fukami T *et al.* (2006) [16636685]
 154. Fuller RW *et al.* (1981) [6268095]
 155. Furet P *et al.* (2013) [23726034]
 156. Furfine ES *et al.* (1995) [7756316]
 157. Furster C *et al.* (1999) [9931427]
 158. Fürstenberger G *et al.* (2002) [12432921]
 159. Galle J *et al.* (1999) [10369473]
 160. Galli A *et al.* (1994) [8039548]
 161. Gangjee A *et al.* (2005) [16078850]
 162. Gangjee A *et al.* (2012) [22739090]
 163. Gao BN *et al.* (1991) [1946437]
 164. Garbarg M *et al.* (1980) [7452304]
 165. Garcia-Manero G *et al.* (2011) [21220589]
 166. Gardner C *et al.* (2000) [10872825]
 167. Garthwaite J *et al.* (1995) [7544433]
 168. Garvey EP *et al.* (1997) [9030556]
 169. Garvey EP *et al.* (1994) [7523409]
 170. Gehrman T *et al.* (1999) [10101268]
 171. Ghafouri N *et al.* (2004) [15492019]
 172. Giacobini E. (2003) [12675140]
 173. Gilmartin AG *et al.* (2011) [21245089]
 174. Gilmzer RI *et al.* (1986) [3457563]
 175. Goding JW *et al.* (2003) [12757929]
 176. Golas JM *et al.* (2003) [12543790]
 177. Golde TE *et al.* (2001) [11378516]
 178. Graf C *et al.* (2008) [18612076]
 179. Graham DW *et al.* (1987) [3495664]
 180. Greengard O *et al.* (1976) [944951]
 181. Gryglewski RJ *et al.* (1976) [824685]
 182. Gryglewski RJ *et al.* (1995) [7778318]
 183. Gschwendt M *et al.* (1996) [8772178]
 184. Gupta R *et al.* (2009) [19149538]
 185. Guranowski A *et al.* (1981) [7470463]
 186. Gustafsson D *et al.* (1998) [9459334]
 187. Haber MT *et al.* (1991) [1654825]
 188. Haefely WE *et al.* (1990) [2122653]
 189. Hammond SM *et al.* (1997) [9013646]
 190. Han G *et al.* (2009) [19416851]
 191. Hanan EJ *et al.* (2012) [23061660]
 192. Handratia VD *et al.* (2005) [15828836]
 193. Hansen JD *et al.* (2008) [18676143]
 194. Harmon SD *et al.* (2006) [16820285]
 195. Hartung IV *et al.* (2013) [23474388]
 196. Hatae T *et al.* (1996) [8766713]
 197. Hatzelmann A *et al.* (1993) [8381000]
 198. Haul NH *et al.* (2002) [11960487]
 199. Hausser A *et al.* (2005) [16100512]
 200. Hayakawa M *et al.* (2007) [17601739]
 201. Hayashi M *et al.* (1998) [9784418]
 202. Hayashi S *et al.* (2004) [15246535]
 203. Hays SJ *et al.* (1998) [9544206]
 204. Heikkilä T *et al.* (2007) [17228860]
 205. Heinemann V *et al.* (1990) [2233693]
 206. Heinrich DM *et al.* (2013) [23454516]
 207. Hepler JR *et al.* (1993) [8314796]
 208. Hess KC *et al.* (2005) [16054031]
 209. Hieke M *et al.* (2011) [21873070]
 210. Hill J *et al.* (2000) [10781930]
 211. Hinz B *et al.* (2008) [17884974]
 212. Hoffmann R *et al.* (1999) [10022832]
 213. Hoffmann R *et al.* (1998) [9639573]
 214. Homma Y *et al.* (1995) [7835339]
 215. Horbert R *et al.* (2015) [26061392]
 216. Horio T *et al.* (2007) [17376680]
 217. Houslay MD *et al.* (2003) [12444918]
 218. Howard S *et al.* (2009) [19143567]
 219. Hsieh AC *et al.* (2012) [22367541]
 220. Huang WS *et al.* (2010) [20513156]
 221. Hubbert C *et al.* (2002) [12024216]
 222. Hughes SA *et al.* (2000) [11138848]
 223. Illenberger D *et al.* (2003) [12441352]
 224. Illenberger D *et al.* (2003) [12509427]
 225. Imiya M *et al.* (1997) [9361377]
 226. Ishida H *et al.* (1992) [1400444]
 227. Ishikawa Y *et al.* (1992) [1618857]
 228. Istvan ES *et al.* (2001) [11349148]
 229. Iverson C *et al.* (2009) [19706763]
 230. Iwami G *et al.* (1995) [7759492]
 231. Izbicka E *et al.* (2009) [19221750]
 232. Jaakkola P *et al.* (2001) [11292861]
 233. Jacobowitz O *et al.* (1993) [8440678]
 234. Jagrat M *et al.* (2011) [21680183]
 235. Janusz JM *et al.* (1998) [9544212]
 236. Jarvis MF *et al.* (2000) [11086253]
 237. Jhon DY *et al.* (1993) [8454637]
 238. Jirousek MR *et al.* (1996) [8709095]
 239. Joh TH *et al.* (1978) [33381]
 240. Johansen PA *et al.* (1996) [8592157]
 241. Johnson J *et al.* (1996) [8603045]
 242. Johnson PH *et al.* (1991) [1894196]
 243. Johnston M *et al.* (2012) [22738638]
 244. Jones CE *et al.* (2003) [12606753]
 245. Jones GH *et al.* (1987) [3027338]
 246. Joshi KS *et al.* (2007) [17363486]
 247. Kalgutkar AS *et al.* (2002) [11844663]
 248. Kameoka J *et al.* (1993) [8101391]
 249. Kang J *et al.* (1987) [2881207]
 250. Kawabe J *et al.* (1994) [8206971]
 251. Kawai S *et al.* (1998) [9650852]
 252. Kedei N *et al.* (2004) [15126366]
 253. Keith JM *et al.* (2008) [18693015]
 254. Khan O *et al.* (2012) [22124371]
 255. Khanna S *et al.* (2012) [23122864]
 256. Kim NN *et al.* (2001) [11258879]
 257. Kimura S *et al.* (2005) [16105974]
 258. Kitagawa D *et al.* (2013) [23279183]
 259. Knight ZA *et al.* (2006) [16647110]
 260. Kobayashi T *et al.* (2004) [15040786]
 261. Koch J *et al.* (1996) [8955159]
 262. Kodimuthali A *et al.* (2008) [18686943]
 263. Koeberle A *et al.* (2008) [19053751]
 264. Kolasa T *et al.* (1997) [9057869]
 265. Kondoh G *et al.* (2005) [15665832]
 266. Kong F *et al.* (2011) [21438579]
 267. Kouzarides T. (2007) [17320507]
 268. Kovacs JJ *et al.* (2005) [15916966]
 269. Kozasa T *et al.* (1998) [9641915]
 270. Krapcho J *et al.* (1988) [2836590]
 271. Krjukova J *et al.* (2004) [15302681]
 272. Kunick C *et al.* (2004) [14698171]
 273. Kupperman E *et al.* (2010) [20160034]
 274. Lahiri S *et al.* (2005) [16100120]
 275. Lai HL *et al.* (1999) [10462552]
 276. Lannutti BJ *et al.* (2011) [20959606]
 277. Laquerre S *et al.* (2009) Abstract B88: A selective Raf kinase inhibitor induces cell death and tumor regression of human cancer cell lines encoding B-RafV600E mutation. *Molecular Cancer Therapeutics* **8**:
 278. Laviad EL *et al.* (2008) [18165233]
 279. Lavieri RR *et al.* (2010) [20735042]
 280. Lazer ES *et al.* (1997) [9083488]
 281. Lee CH *et al.* (1992) [1322889]
 282. Lefebvre HP *et al.* (2007) [17506720]
 283. Leisle L *et al.* (2005) [16270062]
 284. Li W *et al.* (2007) [17629278]
 285. Li X *et al.* (2014) [24915291]
 286. Li-Hawkins J *et al.* (2000) [10748047]
 287. Lim KG *et al.* (2011) [21620961]
 288. Lin RJ *et al.* (2001) [11704848]
 289. Lippert B *et al.* (1977) [856582]
 290. Liu KK *et al.* (2011) [24900269]
 291. Liu Q *et al.* (2010) [20860370]
 292. Liu Q *et al.* (2002) [12047899]
 293. Liu Y *et al.* (2005) [15664519]
 294. Loftus TM *et al.* (2000) [10875926]
 295. Long JZ *et al.* (2009) [19029917]
 296. Look GC *et al.* (1996) *Bioorg Med Chem Letts* **6**: 707-712
 297. Lopez D. (2008) [18836590]
 298. Lopez I *et al.* (1998) [9582313]
 299. Lotta T *et al.* (1995) [7703232]
 300. Loughney K *et al.* (1996) [8557689]
 301. Lunniss CJ *et al.* (2009) [19195882]
 302. Luo J *et al.* (2000) [11099047]
 303. Luo JQ *et al.* (1997) [9207251]
 304. Luo M *et al.* (2004) [15280375]
 305. Luo W *et al.* (2006) [16570913]
 306. Lustig KD *et al.* (1993) [8390980]
 307. Lépine S *et al.* (2011) [22052905]
 308. Ma L *et al.* (2013) [23584399]
 309. Maier SA *et al.* (2005) [16245011]
 310. Maira SM *et al.* (2008) [18606717]
 311. Malerich JP *et al.* (2010) [21106455]
 312. Malmlöf T *et al.* (2015) [24906468]
 313. Manning G *et al.* (2002) [12471243]
 314. Mao C *et al.* (2001) [11356846]

315. Markman B *et al.* (2012) [22357447]
 316. Marrs WR *et al.* (2010) [20657592]
 317. Marsell R *et al.* (2012) [22142634]
 318. Martin MW *et al.* (2006) [16884310]
 319. Martinez GR *et al.* (1992) [1311763]
 320. Mason JM *et al.* (2014) [25043604]
 321. Matsuura K *et al.* (1998) [9792917]
 322. Mayer B *et al.* (1997) [9433128]
 323. Mayhoub AS *et al.* (2012) [22386564]
 324. McAllister G *et al.* (1992) [1377913]
 325. McGaraughty S *et al.* (2001) [11160637]
 326. Meanwell NA *et al.* (1992) [1321910]
 327. Medvedev AE *et al.* (1998) [9564636]
 328. Meldrum E *et al.* (1991) [1848183]
 329. Meyers R *et al.* (1997) [9020160]
 330. Michaeli T *et al.* (1993) [8389765]
 331. Michaud A *et al.* (1997) [9187274]
 332. Michie AM *et al.* (1996) [8730511]
 333. Mishra N *et al.* (2011) [21377879]
 334. Miyake Y *et al.* (1995) [7794249]
 335. Mizukami Y *et al.* (1993) [8389204]
 336. Mizutani Y *et al.* (2005) [15823095]
 337. Mlinar B *et al.* (2003) [14511335]
 338. Mochida H *et al.* (2002) [123450574]
 339. Mohamed HA *et al.* (2011) [21189023]
 340. Moncada S *et al.* (1997) [92286663]
 341. Moore WM *et al.* (1994) [7525961]
 342. Mori S *et al.* (2003) [12939527]
 343. Muftuoglu Y *et al.* (2010) [20413308]
 344. Murthy SN *et al.* (1999) [10518533]
 345. Nagahara N *et al.* (1995) [7608189]
 346. Nagar B *et al.* (2002) [12154025]
 347. Nakamura H *et al.* (2009) [19428245]
 348. Nakano M *et al.* (2009) [19661213]
 349. Nakashima T *et al.* (1978) [748042]
 350. Nakaya Y *et al.* (2011) [22829185]
 351. Nelson PH *et al.* (1990) [1967654]
 352. Nicholson AN *et al.* (1981) [6457252]
 353. Nilsson T *et al.* (2010) [19919823]
 354. Noshiro M *et al.* (1990) [2384150]
 355. Nylander S *et al.* (2012) [22906130]
 356. O'Hare T *et al.* (2005) [15930265]
 357. Ochi T *et al.* (2000) [10720634]
 358. Oh SF *et al.* (2011) [21206090]
 359. Ohnishi T *et al.* (2007) [17068342]
 360. Okada Y *et al.* (2012) [22446963]
 361. Okamoto K *et al.* (2003) [12421831]
 362. Okamoto Y *et al.* (2004) [14634025]
 363. Olesen SP *et al.* (1998) [9489619]
 364. Onda T *et al.* (2001) [11602596]
 365. Osisami M *et al.* (2012) [22428023]
 366. Ottanà R *et al.* (2005) [15993594]
 367. Overington JP *et al.* (2006) [17139284]
 368. Ovarinen AE *et al.* (1979) [438812]
 369. Palanki MS *et al.* (2007) [17685602]
 370. Pan Z *et al.* (2007) [17154430]
 371. Panek RL *et al.* (1997) [9400019]
 372. Papageorgiou C *et al.* (1998) [97196004]
 373. Papamichael D. (1999) [10631692]
 374. Park D *et al.* (1993) [8383116]
 375. Parker WB *et al.* (1991) [1707752]
 376. Paterson JM *et al.* (2000) [10987815]
 377. Paugh SW *et al.* (2008) [18511810]
 378. Pawelczyk T *et al.* (1992) [1497353]
 379. Payne EJ *et al.* (2009) [19470632]
 380. Perzborn E *et al.* (2010) [20139357]
 381. Petersen G *et al.* (1999) [10428468]
 382. Pheneger J *et al.* (2006) Characterization of ARRY-438162, a Potent MEK Inhibitor in Combination with Methotrexate or Ibuprofen in In Vivo Models of Arthritis.[abstract]. *American College of Rheumatology. 2006 Annual Scientific Meeting. Abstract 794*
 383. Philipp S *et al.* (2010) [20080539]
 384. Piechulek T *et al.* (2005) [16172125]
 385. Pinto DJ *et al.* (2010) [20503967]
 386. Pinto-Bazurco Mendieta MA *et al.* (2008) [18672868]
 387. Pireddu R *et al.* (2012) [23275831]
 388. Plourde PV *et al.* (1994) [7949201]
 389. Pollard JR *et al.* (2009) [19320489]
 390. Potter GA *et al.* (1995) [7608911]
 391. Preininger AM *et al.* (2006) [16638972]
 392. Premont RT *et al.* (1996) [8662814]
 393. Purandare AV *et al.* (2012) [22015772]
 394. Qu N *et al.* (2003) [12859253]
 395. Quintás-Cardama A *et al.* (2010) [20130243]
 396. Rabionet M *et al.* (2008) [18308723]
 397. Rameh LE *et al.* (1997) [9367159]
 398. Randall MJ *et al.* (1981) [6795753]
 399. Randall RW *et al.* (1990) [2186929]
 400. Rao NL *et al.* (2010) [20110560]
 401. Rask-Andersen M *et al.* (2014) [24016212]
 402. Rawson DJ *et al.* (2012) [22100260]
 403. Ray P *et al.* (2011) [21145740]
 404. Raynaud FI *et al.* (2009) [19584227]
 405. Riebeling C *et al.* (2003) [12912983]
 406. Riendeau D *et al.* (2001) [11160644]
 407. Ring DB *et al.* (2003) [12606497]
 408. Rivera VM *et al.* (2011) [21482695]
 409. Robinson DM *et al.* (2007) [17547476]
 410. Ropero S *et al.* (2007) [19383284]
 411. Rose KA *et al.* (1997) [9144166]
 412. Rosowsky A *et al.* (1995) [7877140]
 413. Rouault M *et al.* (2003) [14516201]
 414. Sadik CD *et al.* (2003) [12628491]
 415. Saha AK *et al.* (2000) [10854420]
 416. Sahebkar A *et al.* (2014) [25083925]
 417. Saldou N *et al.* (1998) [9720765]
 418. Sarri E *et al.* (2003) [12374567]
 419. Sasaki T *et al.* (2000) [10814504]
 420. Sauve AA. (2010) [20132909]
 421. Schindler U *et al.* (2006) [16332991]
 422. Schmid AC *et al.* (2004) [15474001]
 423. Schmidt M *et al.* (2001) [11715024]
 424. Shahrokh K *et al.* (2010) [20708937]
 425. Schnute ME *et al.* (2012) [22397330]
 426. Schwab SR *et al.* (2005) [16151014]
 427. Sedrani R *et al.* (1998) [9723437]
 428. Semenas J *et al.* (2014) [25071204]
 429. Semenza GL. (2001) [11595178]
 430. Sethi KK *et al.* (2013) [23965175]
 431. Seynaeve CM *et al.* (1994) [8022414]
 432. Shahrokh K *et al.* (2010) [22677141]
 433. Shao J *et al.* (2005) [15670581]
 434. Sharma RK *et al.* (2012) [22628311]
 435. Sharp JD *et al.* (1994) [8083230]
 436. Shih C *et al.* (1998) [9762351]
 437. Silverman RB. (2012) [22168767]
 438. Simon GM *et al.* (2010) [20393650]
 439. Simó-Riudalbas L *et al.* (2014) [24104525]
 440. Simó-Riudalbas L *et al.* (2015) [25039449]
 441. Sinnarajah S *et al.* (2001) [11234015]
 442. Sircar I *et al.* (1989) [2536438]
 443. Sjholt G *et al.* (2000) [10822345]
 444. Sjholt G *et al.* (1997) [9339367]
 445. Skalizky DJ *et al.* (2003) [12519059]
 446. Skarydová L *et al.* (2009) [19007764]
 447. Smith RJ *et al.* (1990) [2338654]
 448. Smith SJ *et al.* (2004) [15371556]
 449. Smrcka AV *et al.* (1991) [1846707]
 450. Snider NT *et al.* (2010) [20133390]
 451. Solorzano C *et al.* (2009) [19926854]
 452. Song C *et al.* (2001) [11022048]
 453. Sontag TJ *et al.* (2002) [11997390]
 454. Sperzel M *et al.* (2007) [17666018]
 455. Stanek J *et al.* (1993) [8340919]
 456. Stanek J *et al.* (1992) [1573631]
 457. Stanley LA. (1995) [7900159]
 458. Stanley WC *et al.* (1997) [9283721]
 459. Stark K *et al.* (2008) [18549450]
 460. Stasch JP *et al.* (2001) [11242081]
 461. Stasch JP *et al.* (2002) [12086987]
 462. Steinberg D *et al.* (2009) [19506257]
 463. Stevens T *et al.* (2011) [21791628]
 464. Stoilov I *et al.* (1997) [9097971]
 465. Sudo T *et al.* (2000) [10644042]
 466. Sun W *et al.* (2008) [17713573]
 467. Sutherland DP *et al.* (2011) [21981714]
 468. Suzuki T *et al.* (2013) [23577190]
 469. Tai AW *et al.* (2011) [21704602]
 470. Takahashi T *et al.* (2012) [22386242]
 471. Takasugi N *et al.* (2003) [12660785]
 472. Takeuchi CS *et al.* (2013) [23394126]
 473. Talley JJ *et al.* (2000) [10715145]
 474. Tang WJ *et al.* (1991) [2022671]
 475. Tani M *et al.* (2003) [12499379]
 476. Tani M *et al.* (2009) [19233134]
 477. Tanizawa A *et al.* (1994) [8182764]
 478. Taussig R *et al.* (1993) [8416978]
 479. Taussig R *et al.* (1994) [8119955]
 480. Taylor A. (1993) [8440407]
 481. Teigen K *et al.* (2004) [15537351]
 482. Temperini C *et al.* (2009) [19119014]
 483. Tenu JP *et al.* (1999) [10637120]
 484. Terao C *et al.* (2013) [23124809]
 485. Tesmer JJ *et al.* (2000) [11087399]
 486. Thilagavathi R *et al.* (2005) [15686906]
 487. Thomas M *et al.* (2011) [21561767]
 488. Thompson JF *et al.* (1998) [9473303]
 489. Toprakçi M *et al.* (2005) [16137882]
 490. Toullec D *et al.* (1991) [1874734]
 491. Tseng WC *et al.* (1982) [7048062]
 492. Tsuboi K *et al.* (2004) [14686878]
 493. Tuccinardi T *et al.* (2006) [16483784]
 494. Turko IV *et al.* (1999) [10385692]
 495. Ueda N *et al.* (2001) [11463796]
 496. Uehata M *et al.* (1997) [9353125]
 497. Van Rompaey L *et al.* (2013) [24006460]
 498. Vemulapalli S *et al.* (1996) [8961086]
 499. Venkataraman K *et al.* (2002) [12105227]
 500. Venkatesan AM *et al.* (2010) [20166697]
 501. Verma RP *et al.* (2007) [17275314]
 502. Vethe NT *et al.* (2008) [18609073]
 503. Viegas A *et al.* (2011) [22091869]
 504. Vullo D *et al.* (2005) [15686894]
 505. WILSON IB *et al.* (1961) [13785664]
 506. Wagner J *et al.* (2009) [19827831]

507. Walliser C *et al.* (2008) [[18728011](#)]
508. Wang P *et al.* (1997) [[9177268](#)]
509. Wang T *et al.* (2011) [[21493067](#)]
510. Wang X *et al.* (2012) [[22808911](#)]
511. Warkentin TE *et al.* (2005) [[16363236](#)]
512. Warner TD *et al.* (1999) [[10377455](#)]
513. Watanuki M *et al.* (1978) [[412519](#)]
514. Waterfall JF. (1989) [[2527528](#)]
515. Watermeyer JM *et al.* (2010) [[20233165](#)]
516. Watson PA *et al.* (1994) [[7961850](#)]
517. Wayman GA *et al.* (1995) [[7665559](#)]
518. Wei BQ *et al.* (2006) [[17015445](#)]
519. Weiler S *et al.* (2014) [[24809814](#)]
520. Wells RA *et al.* (2014) [[24523604](#)]
521. Wernig G *et al.* (2008) [[18394554](#)]
522. West AC *et al.* (2014) [[24382387](#)]
523. Wilensky RL *et al.* (2009) [[19667981](#)]
524. Wilkerson WW *et al.* (1995) [[7562922](#)]
525. Wing MR *et al.* (2003) [[14993441](#)]
526. Wittine K *et al.* (2012) [[22555152](#)]
527. Witting JI *et al.* (1992) [[1290488](#)]
528. Wong PC *et al.* (2008) [[18315548](#)]
529. Wu F *et al.* (2010) [[20462760](#)]
530. Wu JY *et al.* (1973) [[4700449](#)]
531. Wu S *et al.* (1996) [[8631948](#)]
532. Wuerzner G *et al.* (2008) [[18307734](#)]
533. Xie S *et al.* (2010) [[21049984](#)]
534. Xu R *et al.* (2006) [[16940153](#)]
535. Yaguchi S *et al.* (2006) [[16622124](#)]
536. Yamaguchi T *et al.* (2011) [[21523318](#)]
537. Yin L *et al.* (2014) [[24899257](#)]
538. Yoshida S *et al.* (2004) [[15110846](#)]
539. Yoshikawa F *et al.* (2010) [[21085684](#)]
540. Yoshikawa T *et al.* (1997) [[9322233](#)]
541. Yoshimura M *et al.* (1992) [[1379717](#)]
542. Youdim MB *et al.* (2001) [[11159700](#)]
543. Yu Z *et al.* (2003) [[12881489](#)]
544. Zabel U *et al.* (1998) [[9742212](#)]
545. Zambon A *et al.* (2012) [[22222036](#)]
546. Zavalov AV *et al.* (2010) [[20147294](#)]
547. Zeldin DC *et al.* (1995) [[7574697](#)]
548. Zhang HQ *et al.* (1997) [[9397167](#)]
549. Zhang J *et al.* (2010) [[20072125](#)]
550. Zhang J *et al.* (2007) [[17721087](#)]
551. Zhou Y *et al.* (2005) [[16107206](#)]
552. Zhu MY *et al.* (2004) [[14738999](#)]
553. Zimmer C *et al.* (2011) [[21129965](#)]
554. Zimmermann G *et al.* (1996) [[8900209](#)]
555. Zimmermann TJ *et al.* (2009) [[19097799](#)]